4-Phenyl- and 4-Heteroaryl-4-anilidopiperidines. A Novel Class of Analgesic and Anesthetic Agents[1]

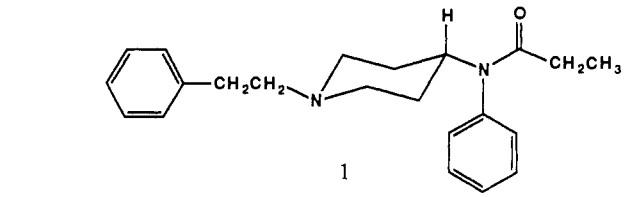
Linas V. Kudzma,*,† Sherry A. Severnak,† Mark J. Benvenga,‡ Edward F. Ezell,§ Michael H. Ossipov,‡ Valerie V. Knight,‡ Frieda G. Rudo,∥ H. Kenneth Spencer,† and Theodore C. Spaulding‡

Anaquest and The BOC Group, Inc., BOC Group Technical Center, 100 Mountain Ave., Murray Hill, New Jersey 07974, and Department of Pharmacology, School of Dentistry, University of Maryland, Baltimore, Maryland 21201.
Received February 16, 1989

The incorporation of the 4-phenylpiperidine pharmacophore found in morphine into 4-anilidopiperidines related to fentanyl (1) led to a novel class of potent opioid analgesic and anesthetic agents with a favorable pharmacological profile. The synthesis, analgesic activity, and anesthetic properties of a series of 4-phenyl-4-anilidopiperidines (13–29) are discussed. Isosteric replacement of the phenyl by various heteroaryl substituents extended the series to include 4-heteroaryl-4-anilidopiperidines (30–53). Within this group, 1-[2-(1*H*-pyrazol-1-yl)ethyl]-4-(4-methylthiazol-2-yl)-4-(*N*-phenylpropionamido)piperidine (48), exhibited high analgesic potency, short duration of action, rapid recovery of motor coordination following anesthetic doses, and greater cardiovascular and respiratory safety during anesthesia as compared with opioids fentanyl (1) and alfentanil (2) currently in clinical use. Such analgesics could be of great utility to clinicians in the expanding outpatient surgical arena and for patient-controlled analgesia and computer assisted continuous infusion pain control techniques.

The 4-anilidopiperidine class of synthetic opioid analgesics is characterized by high potency and rapid onset of action. Fentanyl (1)[2] is the prototype of the series. Intravenous infusion of 1 concurrent with a skeletal muscle relaxant and an inhalation anesthetic is a widely accepted practice in surgical procedures. Expansion of the structure–activity relationships (SAR) of the 4-anilidopiperidines has led to the discovery of new morphinomimetics with diverse analgesic profiles. Particularly significant is the recent development of alfentanil (2).[3] Although a less potent analgesic, 2 has a more rapid onset, shorter duration of action, and a less severe respiratory depressant effect[4,5] than 1. Due to the rise in the number of outpatient surgical procedures, short-acting analgesics with less severe untoward opioid side effects such as respiratory and cardiovascular depression are in high demand to allow patients to be ambulatory. Such analgesics would also be useful in patient-controlled analgesia (PCA) as well as computer assisted continuous infusion (CACI) pain control techniques.

The 4-phenylpiperidine pharmacophore embedded in the structure of morphine (3) is a central feature in many analgesics acting at the opioid receptor.[6] Herein, we report the synthesis of a series of 4-phenyl-4-anilidopiperidines of type 4, which incorporate this pharmacophore and exhibit a favorable pharmacological profile. Most notable was a very rapid recovery of normal motor coordination following doses sufficient to induce a transient loss of righting. Replacement of the 4-phenyl substituent of these compounds with various heteroaromatics was a natural extension of this novel series. A number of the resultant 4-heteroaryl-4-anilidopiperidines also exhibited high potency and a markedly superior anesthetic syndrome and recovery as compared to alfentanil (2).



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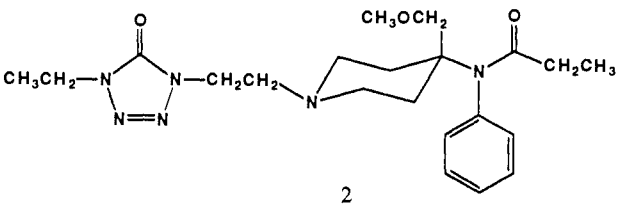

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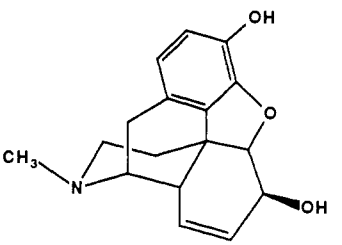

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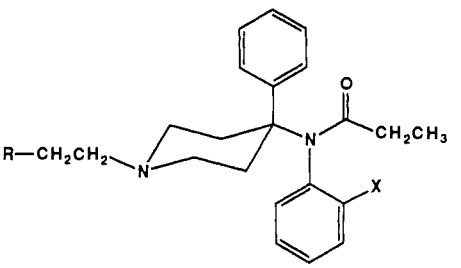

4

Chemistry

4-Phenyl-4-anilidopiperidines described in this study were synthesized as outlined in Scheme I. The appropriate aniline was condensed with 1-benzyl-4-piperidone, and the resultant imines 5 were treated with phenyllithium to afford 4-phenyl-4-anilinopiperidines 7a–c. Acylation of these hindered diamines with propionyl chloride proved to be troublesome. Attempts to promote acylation at higher temperature (refluxing neat propionic anhydride, 167 °C) resulted in decomposition. However, prolonged

* Author to whom correspondence should be addressed.
† Department of Chemistry, Anaquest.
‡ Department of Pharmacology, Anaquest.
§ The BOC Group, Inc.
∥ Department of Pharmacology, University of Maryland.

(1) A preliminary account of this work has been presented: 21st National Medicinal Chemistry Symposium of the American Chemical Society, Minneapolis, Minnesota, June 19–23, 1988; Abstract 9.
(2) Fentanyl citrate, Sublimaze, McNeil Laboratories, Inc. Janssen, P. A. J. U.S. Patent 3,164,600, 1965.
(3) (a) Janssen, P. A. J. *Br. J. Anaesth.* **1962**, *34*, 260. (b) Gardocki, J. K.; Yelnosky, J.; Kuehn, W. F.; Gunster, H. *Toxicol. Appl. Pharmacol.* **1964**, *6*, 593.
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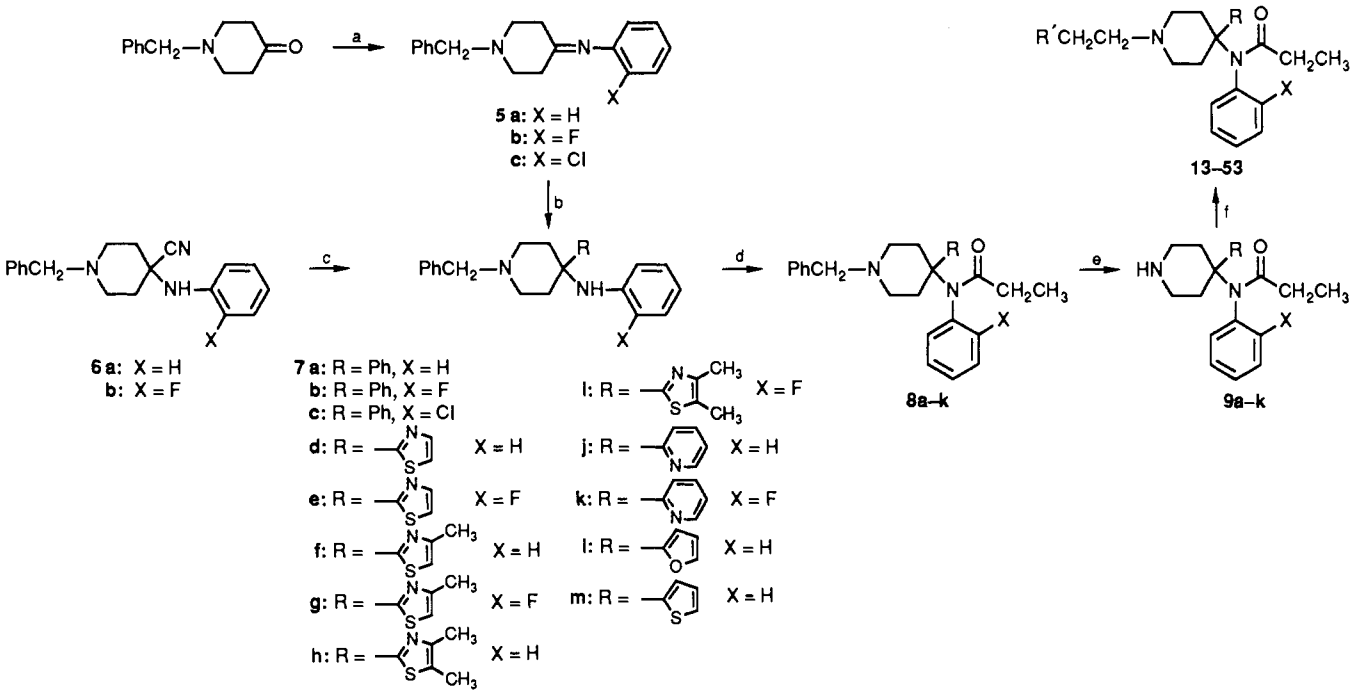
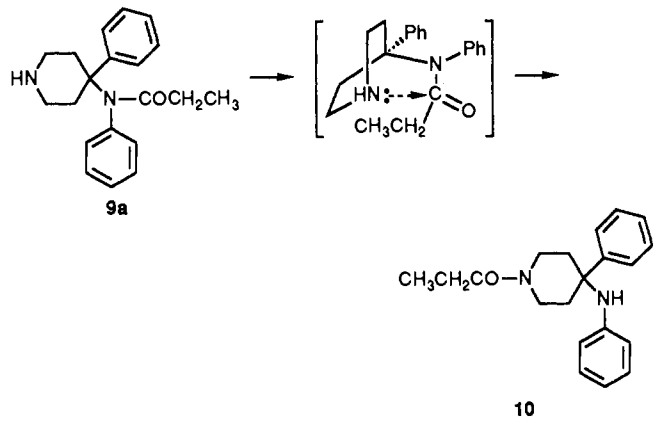
Scheme I[a]

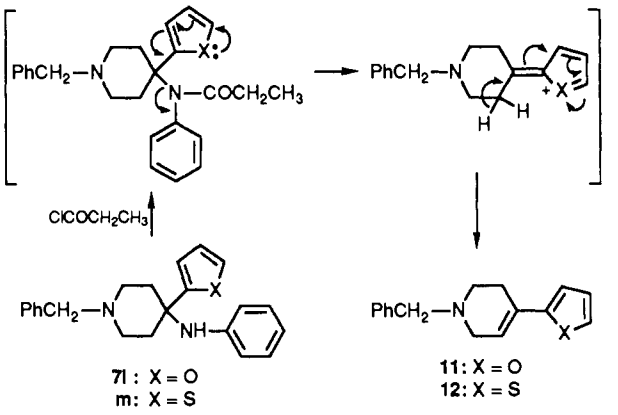


[a] (a)  , *p*-TsOH, toluene, Δ; (b) PhLi, cyclohexane/Et_2O 7:3, 0 °C; (c) RLi, THF, −78 °C; (d) $ClCOCH_2CH_3$, $CHCl_3$, Δ; (e) (1) ACE-Cl, $ClCH_2CH_2Cl$, Δ; (2) MeOH, Δ; (f) $R'CH_2CH_2Br$ or OTS, CH_3CN, K_2CO_3.

Scheme II



Scheme III



reflux (1–2 weeks) with a large excess of propionyl chloride in chloroform gradually afforded the desired amides **8a–c** in high yield. The benzyl protecting group was removed by treatment with 1-chloroethyl chloroformate (ACE-Cl)[7] followed by methanolysis. The resultant secondary amines **9a–c** were observed to undergo a facile acyl migration at room temperature, most likely via a six-membered transition state (Scheme II), similar to one described by Colapret et al.[8] Analogous O to N acyl migrations in prodine derivatives have been described by Portoghese et al.[9]

Amines **9a–c** were therefore immediately (without purification) treated with the appropriate arylethyl halides or tosylates to give the desired compounds **13–29**.

α-Aminonitriles **6**[10] were prepared via the Strecker synthesis. 4-Heteroaryl-4-anilinopiperidines **7d–m** were prepared from the appropriate α-aminonitriles and lithiated heterocycles via a variant of the Bruylants reaction as previously described.[11] While the 4-phenyldiamines **7a–c** were most efficiently prepared via the imines **5**, the α-aminonitrile route proved to be the method of choice for the synthesis of 4-heteroaryldiamines **7d–k**. These 4-heteroaryldiamines **7d–k** were less resistant to acylation than the 4-phenyldiamines and were treated with propionyl chloride in refluxing chloroform for 1–3 days to afford the desired amides **8d–k** in high yield. The acylation of 4-(2-furoyl)-4-anilinopiperidine **7l** and 4-(2-thie-

(5) Reviewed in: Hug, C. C.; Chaffman, M. *Alfentanil: Pharmacology and Uses in Anaesthesia*; Camu, F., Spierdijk, J., Eds.; ADIS Press: Auckland, New Zealand, 1984.
(6) Reviewed in: Lednicer, D. *Medicinal Chemistry of Central Analgesics*; Wiley-Interscience: New York, 1982.
(7) Olofson, R. A.; Martz, J. T. *J. Org. Chem.* **1984**, *49*, 2081.
(8) Colapret, J. A.; Diamantidis, G.; Spencer, H. K.; Spaulding, T. C. *J. Med. Chem.* **1989**, *32*, 968.
(9) (a) Abdel-Monem, M. M.; Larson, D. L.; Kupferberg, H. J.; Portoghese, P. S. *J. Med. Chem.* **1972**, *15*, 494. (b) Abdel-Monem, M. M.; Harris, P. A.; Portoghese, P. S. *J. Med. Chem.* **1972**, *15*, 706.
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nyl)-4-anilinopiperidine **7m** failed to give the desired amides but rather the products **11** and **12**. They most likely arise via the mechanism proposed in Scheme III, in which an electron pair of oxygen or sulfur in the heterocycle assists in the elimination of the anilido group followed by loss of a proton from the piperidine to produce **11** and **12**. An analogous loss of an ester upon acylation of 4-(2-furyl)-4-hydroxypiperidines has been described.[12]

Amides **8d–k** were debenzylated and alkylated as shown in Scheme I to give the compounds **30–53**. All compounds evaluated for biological activity were tested as their oxalate salts crystallized from methanol/*tert*-butyl methyl ether. Oxalate salts are typically highly crystalline and nonhygroscopic and have proven to be the most practical vehicle for parenteral administration of 4-anilidopiperidines to laboratory animals.[13] No toxicity due to oxalic acid was observed at the low doses used for this study.

Results and Discussion

Morphine and many related opioid analgesics share a common overlap of a phenyl ring and an amine nitrogen which is two carbon atoms removed from a quaternary carbon. Beckett and Casy[14] first described 4-phenylpiperidine in a chair conformation with the phenyl ring situated axially as being a common pharmacophore in opioid analgesics. However, this model is not applicable to certain cases, most notably the 4-anilidopiperidine fentanyl (**1**), although 300 times as potent as morphine (in tail-withdrawal tests in rats[15]), lacks the 4-phenylpiperidine pharmacophre or any obvious isomorphic chemical connectivity relationship to morphine.

Attempting to describe a single mode of association to the opioid receptor site capable of accounting for all the structural features of the various classes of opioid analgesics is not necessary, since not all compounds need to have the same association at the receptor. Portoghese[16] has shown that 4-phenylpiperidine analgesics may interact with the receptor with the phenyl group adopting either an axial or an equatorial orientation. Furthermore, it has been shown by Lobbezoo[17] and Reden et al.[18] that it is unlikely, with respect to drug–receptor interaction, that the anilido phenyl ring in 4-anilidopiperidines such as fentanyl (**1**) would correspond with the phenyl ring in morphine. Differences in SAR for the anilido phenyl ring substitution in fentanyl and the phenyl ring substitution of morphine and other 4-phenylpiperidine analgesics suggest that these two distinct classes of analgesics have different modes of association with the opioid receptor. Additionally, proposed binding modes for the enkephalins[19] accommodate the frequent occurrence of a second phenyl ring in the more potent analgesics and relate this group to the phenylalanine side chain of the enkephalins.

Although a 4-phenylpiperidine substructure found in morphine and related analgesics is not a requirement for analgesic activity in fentanyl (**1**), we undertook the synthesis of 4-phenyl-4-anilidopiperidines **13–29** to probe

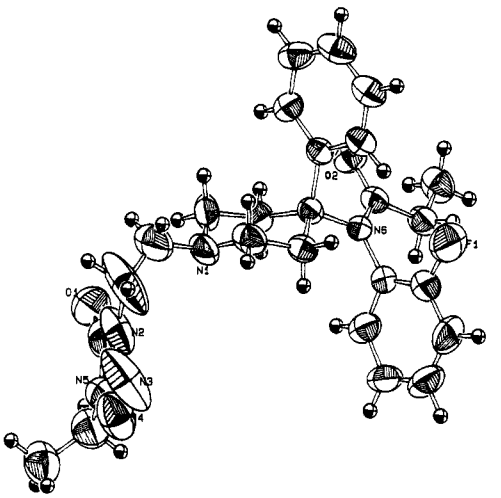

Figure 1. Crystal structure of compound **20**.

binding modes of this hybrid class, and to determine what effect the additional phenyl has on analgesic potency. Single-crystal X-ray diffractometry (Figure 1) of a representative compound, **20**, showed the phenyl at the 4-position of the piperidine to be axially oriented in the solid state. The 4-anilido moiety adopts an equatorial conformation akin to the solid and probable solute-state conformation of fentanyl.[20]

The series of 4-phenyl-4-anilidopiperidines **13–29** were found to posses high analgesic potency. Analgesia of a representative compound (**20**) was reversed by the opioid antagonist naloxone (0.1 mg/kg iv) in rat tail flick and hot plate tests. Variations of analgesic efficacy within the series was a function of the substituents on the piperidine nitrogen and the anilido phenyl. An o-fluoro substituent on the anilido phenyl enhanced analgesic potency, while a chloro substituent diminished analgesia. This substituent effect for analgesia (F > H > Cl) is clearly illustrated in compounds **19–21** (Table I). A similar effect has also been demonstrated in other 4-anilidopiperidines[21] and further substitutions were not investigated in this study.

The most potent analgesics had a phenylethyl, 2-thienylethyl, or 3-thienylethyl substituent on the piperidine nitrogen. Replacement of the phenylethyl or thienylethyls with other heteroarylethyl N-substituents (**19–29**) generally reduced potency. However, all were analgesics at submilligram doses. The 2-(4-ethyl-4,5-dihydro-5-oxo-1*H*-tetrazol-1-yl)ethyl N-substitution not only lowered analgesic potency but also resulted in less respiratory depression (compared to alfentanil) and rapid recovery of normal motor coordination following anesthetic doses of **20**. These effects are discussed in detail at the end of this section.

It was found that the phenyl at the 4-position of the piperidine can be replaced by certain heterocycles without diminishing analgesia. Substituting a 2-pyridyl heteroaryl ring for the 4-phenyl ring gave 4-(2-pyridyl)-4-anilidopiperidines **30–35**, which had similar analgesic potencies to their 4-phenyl counterparts. Further modifications revealed that the phenyl can also be replaced by five-

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(17) Lobbezoo, M. W.; Soudijn, W.; van Wijngaarden, I. *J. Med. Chem.* **1981**, *24*, 777.
(18) Reden, J.; Reich, M. F.; Rice, K. C.; Jacobson, A. E.; Brossi, A.; Stready, R. A.; Klee, W. A. *J. Med. Chem.* **1979**, *22*, 256.
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(20) (a) Janssen, P. A. J.; Tollenaere, J. P. In *Neurochemical Mechanisms of Opiates and Endorphins* (Advances in Biochemistry and Psychopharmacology, Vol. 20); Loh, H. H., Ross, D. H., Eds.; Raven Press: New York, 1979; p 103. (b) Peeters, O. M.; Blaton, N. M.; de Ranter, J.; van Herk, A. M.; Goubitz, K. *J. Crystallogr. Mol. Struct.* **1979**, *9*, 153.
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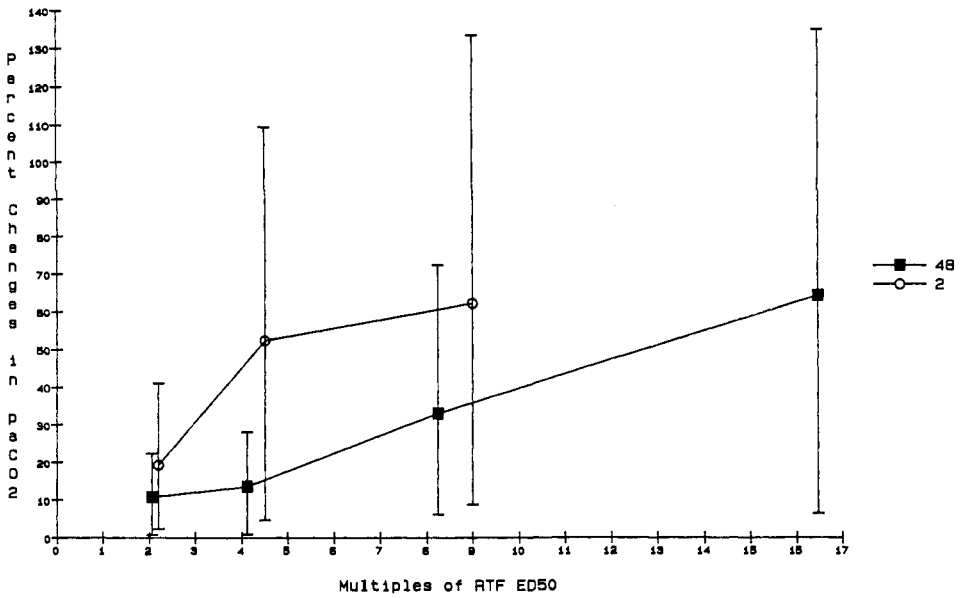


Figure 2. Effects on respiration in conscious, freely moving rats after IV administration of alfentanil (**2**) and **48**. $paCO_2$ = pressure (mmHg) of CO_2 gas in arterial blood. respiratory effects were measured as percent changes in $paCO_2$ after control blood samples were taken, and each animal served as its own control. Data points are means (±SEM), N = 2–5.

membered heteroaryl rings and remain potent analgesics. 4-(Thiazol-2-yl)-4-anilidopiperidines **35** and **36** were among the most potent analgesics synthesized for this study. 4-Methylthiazol-2-yl substitution at the 4-position of the piperidine also gave potent analgesics **40–50**. However, a 4,5-dimethylthiazole ring at the 4-position of the piperidine markedly reduced analgesic potency. Therefore, compounds **51–53** were not extensively investigated. Compound **48**, which bears 2-(1*H*-pyrazol-1-yl)ethyl and 4-methylthiazol-2-yl substituents at the 1- and 4-positions of the piperidine, respectively, was investigated in more detail. As in the 4-phenyl case, analgesia of compound **48** was reversed by naloxone (0.1 mg/kg iv) in rat tail flick and hot plate tests.

Recovery of motor coordination immediately following the righting reflex after anesthetic doses was evaluated in rats by a variation of the rotorod method first described by Kinnard and Carr,[22] and a rotorod index (ROI) was calculated for each compound tested (see the Pharmacological Methods section). The results of the rotarod assessment are indicated in Table II. The between-drug comparison (Kruskal–Wallis H statistic)[23] revealed a significant effect, $H(4) = 6.57$, $p = 0.05$ for the entire group. The subsequent Mann–Whitney U tests[23] revealed a significant difference between alfentanil (**2**) and **20**, and **2** and **48**. There were no other paired differences in the group.

The ROI calculated over the three time intervals were markedly different, ranging from 26.7 for **32** to a perfect 60.0 for **48**. Of the animals who were administered alfentanil (**2**) (ROI = 31.3), only one of five were able to remain on the rod during the first interval, and only two succeeded during the entire test session. All animals succeeded during the first time interval for **48**, and four of the five succeeded in the first time interval for **20**. The ROI's for **20** (57.5) and **48** (60.0) revealed a more rapid recovery than for alfentanil (**2**).

In addition to exceptionally rapid recovery of motor coordination, **48** showed a shorter duration of action than **2**. Durations of analgesia were determined using the 55 °C mouse hot plate assay. A test compound was defined to be short acting if the duration of action to 50% maximum pharmacological effect (MPE) at 16 × ED_{50} dose was less than 15 min. Intermediate duration was defined at 15–25 min, and long duration was defined as greater than 25 min to 50% MPE. 4-Phenyl compound **20** had an intermediate duration of action of 18.5 min, while **48** had a shorter duration (7.5 min) than alfentanil (**2**) (10.4 min), which has the shortest duration of action of all opioids in clinical use.

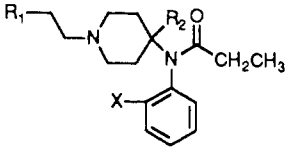
Cardiovascular and respiratory effects were evaluated in conscious, freely moving rats as described in the methods section. In the conscious-rat model, both **20** and **48** showed significantly less respiratory depression than the clinically employed opioids **1** and **2**. Compound **48** required approximately three times the rat tail flick ED_{50} dose of alfentanil (**2**) to elicit an increase in arterial carbon dioxide levels of greater than 50% (Figure 2).

The superiority of **48** in the conscious rat relative to compounds currently in clinical use prompted further investigation of cardiorespiratory effects of this compound. An anesthetized, mechanically ventilated rat model was used to compare cardiovascular effects of compound **48** and **2** in the absence of any significant behavior normally associated with conscious, freely moving rats. These experiments are described in detail in the methods section and are nearly identical with the clinical "operating room" setting. The therapeutic safety index of **48** in depression of mean arterial blood pressure approximated that of compound **2**; however, **48** caused markedly less depression of heart rate. A 35% ceiling effect was observed in depression of heart rate, which precluded calculation of a therapeutic index for depression of heart rate by **48**. Such a ceiling effect was not observed with the clinical agents **1** and **2**.

In conclusion, the incorporation of the 4-phenylpiperidine pharmacophore in 4-anilidopiperidines led to a novel series of 4-phenyl-4-anilidopiperidines which exhibited high analgesic potency and favorable pharmacological properties. The analgesia of representative examples of both the 4-phenyl (**20**) and 4-heteroaryl (**48**) series was reversed by naloxone. Although the phenyl at the 4-position of the piperidine is not a requirement for analgesic activity, such 4,4-disubstituted piperidines are

(22) Kinnard, W. J., Jr.; Carr, C. J. *J. Pharmacol. Exp. Ther.* **1957**, *121*, 354.
(23) Siegal, S. *Nonparametric Statistics*; McGraw-Hill: New York, 1956.

Table I. Analgesic Activity of 4-Phenyl- and 4-Heteroaryl-4-anilidopiperidines



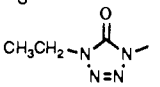
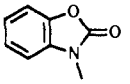
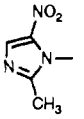
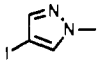
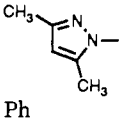
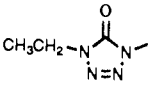
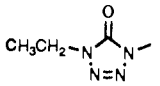
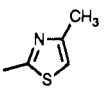
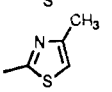
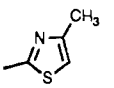
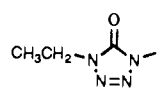
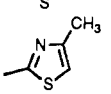
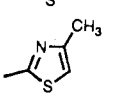
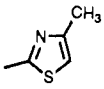
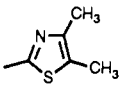
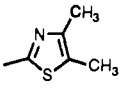
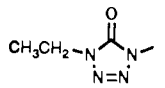
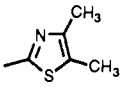
entry	R_1	R_2	X	mp,[a] °C	formula[b]	ED_{50},[c] mg/kg
13	Ph	Ph	H	223–224	$C_{28}H_{32}N_2O \cdot C_2H_2O_4$	0.011 (0.006–0.02)
14	Ph	Ph	F	207–208	$C_{28}H_{31}N_2FO \cdot C_2H_2O_4$	0.0145 (0.0093–0.0228)
15		Ph	H	205–206	$C_{26}H_{30}N_2OS \cdot C_2H_2O_4$	0.014 (0.011–0.02)
16		Ph	F	199–201	$C_{26}H_{29}FN_2OS \cdot C_2H_2O_4$	0.0066 (0.0054–0.008)
17		Ph	H	222–224	$C_{26}H_{30}N_2OS \cdot C_2H_2O_4$	0.0014 (0.0007–0.003)
18		Ph	F	199–201	$C_{26}H_{29}N_2FOS \cdot C_2H_2O_4$	0.0082 (0.0063–0.01)
19		Ph	H	183–185	$C_{25}H_{32}N_6O_2 \cdot C_2H_2O_4$	0.275 (0.223–0.338)
20		Ph	F	200	$C_{25}H_{31}N_6FO_2 \cdot C_2H_2O_4$	0.082 (0.007–0.69)
21		Ph	Cl	186–187	$C_{25}H_{31}N_6ClO_2 \cdot C_2H_2O_4$	0.534 (0.447–0.637)
22		Ph	H	193–195	$C_{25}H_{30}N_4O \cdot C_2H_2O_4$	0.043 (0.030–0.061)
23		Ph	F	200–202	$C_{25}H_{29}N_4FO \cdot C_2H_2O_4$	0.026 (0.02–0.034)
24		Ph	H	174–175	$C_{27}H_{31}N_3O \cdot C_2H_2O_4$	0.026 (0.018–0.037)
25		Ph	F	216–218	$C_{29}H_{30}N_3FO_3 \cdot C_2H_2O_4$	0.435 (0.355–0.534)
26		Ph	F	227–228	$C_{26}H_{30}N_3FOS \cdot C_2H_2O_4$	0.0074 (0.0047–0.011)
27		Ph	F	225	$C_{26}H_{30}N_5FO_3 \cdot C_2H_2O_4$	0.175 (0.134–0.229)
28		Ph	F	219–220	$C_{25}H_{28}N_4FIO \cdot C_2H_2O_4$	0.023 (0.013–0.041)
29		Ph	F	202–203	$C_{27}H_{33}H_4FO \cdot C_2H_2O_4$	0.014 (0.011–0.017)
30	Ph		H	193–194	$C_{27}H_{31}N_3O \cdot C_2H_2O_4$	0.013 (0.01–0.017)
31	Ph		F	216	$C_{27}H_{30}N_3FO \cdot C_2H_2O_4$	0.01 (0.0062–0.016)
32			H	166–167	$C_{24}H_{31}N_7O_2 \cdot C_2H_2O_4$	0.435 (0.355–0.534)
33			F	180–181	$C_{24}H_{30}N_7FO_2 \cdot C_2H_2O_4$	0.115 (0.088–0.150)
34			H	183–184	$C_{24}H_{29}N_5O \cdot C_2H_2O_4$	0.167 (0.131–0.213)
35			F	180–182	$C_{24}H_{28}N_5FO \cdot C_2H_2O_4$	0.059 (0.044–0.081)
36	Ph		H	193–194	$C_{25}H_{29}N_3OS \cdot C_2H_2O_4$	0.0047 (0.034–0.065)
37	Ph		F	202–203	$C_{25}H_{28}N_3FOS \cdot C_2H_2O_4$	0.0034 (0.0028–0.004)
38			H	169–170	$C_{22}H_{29}N_7O_2S \cdot C_2H_2O_4$	0.212 (0.133–0.337)
39			F	177–178	$C_{22}H_{28}N_7FO_2S \cdot C_2H_2O_4$	0.057 (0.042–0.078)
40	Ph		H	204	$C_{26}H_{31}N_3OS \cdot C_2H_2O_4$	0.012 (0.009–0.017)
41	Ph		F	203–204.5	$C_{26}H_{30}N_3FOS \cdot C_2H_2O_4$	0.022 (0.018–0.039)
42			H	181	$C_{24}H_{29}N_3OS_2 \cdot C_2H_2O_4$	0.011 (0.007–0.017)
43			F	198–200	$C_{24}H_{28}N_3FOS_2 \cdot C_2H_2O_4$	0.012 (0.0095–0.015)
44			H	182–183	$C_{24}H_{29}N_3OS_2 \cdot C_2H_2O_4$	0.013 (0.012–0.014)
45			F	202–204	$C_{24}H_{28}N_3FOS_2 \cdot C_2H_2O_4$	0.0059 (0.0045–0.077)
46			H	154–155	$C_{23}H_{31}N_7O_2S \cdot C_2H_2O_4$	0.264 (0.164–0.423)
47			F	144–146	$C_{23}H_{30}N_7FO_2S \cdot C_2H_2O_4$	0.179 (0.132–0.243)
48			H	185–187	$C_{23}H_{29}N_5OS \cdot C_2H_2O_4$	0.064 (0.051–0.079)
49			F	183–185	$C_{23}H_{28}N_5FOS \cdot C_2H_2O_4$	0.047 (0.041–0.055)

Table I (Continued)

entry	R_1	R_2	X	mp,[a] °C	formula[b]	ED_{50},[c] mg/kg
50			F	225	$C_{24}H_{29}N_4FOS_2 \cdot C_2H_2O_4$	0.017 (0.009–0.030)
51	Ph		H	191–192	$C_{27}H_{33}N_3OS \cdot C_2H_2O_4$	>5[d]
52			H	201–202	$C_{25}H_{31}N_3OS_2 \cdot C_2H_2O_4$	0.525 (0.329–0.838)
53			H	194–195	$C_{24}H_{33}N_7O_2S \cdot C_2H_2O_4$	>5[d]
1 (fentanyl)						0.018 (0.014–0.023)
2 (alfentanil)						0.047 (0.034–0.065)

[a] Oxalates crystallized from methanol/*tert*-butyl methyl ether. [b] Elemental analyses were within 0.4% of the theoretical values for C, H, and N. [c] 55 °C mouse hot plate ED_{50} with 95% confidence limits in parentheses. [d] Inactive up to a dose of 5 mg/kg.

Table II. Analgesia and Recovery of Motor Coordination in Rates

			rat rotarod assay (at T = 0 s)		
entry	rat hot plate: ED_{50},[a] mg/kg	rat tail flick: ED_{50},[a] mg/kg	median rotorod duration	range	ROI
(1) fentanyl	0.0086 (0.0056–0.0131)	0.0043 (0.003–0.0061)	3.4	0.9–42.0	18.2
(2) alfentanil	0.0311 (0.011–0.838)	0.0106 (0.078–0.0144)	14.3	2.0–90.0	31.13
20	0.0296 (0.0263–0.0335)	0.0075 (0.0051–0.0109)	90.0[b]	53.0–90.0	57.5
32	0.243 (0.200–0.295)	0.156 (0.123–0.198)	14.1	9.2–90.0	26.7
47	0.077 (0.0614–0.0962)	0.068 (0.053–0.087)	90.0	39.9–90.0	51.6
48	0.055 (0.036–0.086)	0.017 (0.012–0.023)	90.0[b]	0	60.0

[a] 95% confidence limits in parentheses. [b] Mann–Whitney U test revealed significant difference from alfentanil (**2**).

Table III. Cardiorespiratory Effects of 48 and Alfentanil in Forane-Anesthetized Rats

	48: percent change from control			alfentanil (**2**): percent change from control	
dose × RTF ED_{50}[a]	MAP[b]	HR[c]	dose × RTF ED_{50}	MAP	HR
1.0	−13.8 (±8.56)	−12.3 (±10.5)	0.5	−30.81 (±6.29)	−17 (±3)
3.2	−41.5 (±9.68)	−35.8 (±22.3)	4.0	−38.33 (±9.69)	−18 (±4)
6.5	−44.4 (±5.55)	−35.0 (±5.87)	8.0	−38.29 (±1.42)	−25 (±4)
13.0	−52.4 (±12.6)	−20.5 (±8.02)	16.0	−41.79 (±5.11)	−37 (±11)

Therapeutic Indices[d]

	48: percent change from control		alfentanil (**2**): percent change from control	
dose × RTF ED_{50}[a]	MAP[b]	HR[c]	MAP	HR
RTF	10.4	ND[e]	5.0	15.4
RHP	3.2	ND	3.2	9.4

[a] Multiples of rat tail flick ED_{50} values. Three animals were tested per dose. [b] Mean arterial pressure. [c] Heart rate. [d] Therapeutic indices were calculated by dividing the dose which elicited a 50% response from control of either MAP or HR (which was determined graphically) by the RTF (rat tail flick) or RHP (rat hot plate) ED_{50}. [e] Not determinable since a 35% ceiling effect was observed.

accepted by the opioid receptor. Additionally, replacement of the phenyl by certain six- and five-membered heteroaryl rings did not diminish analgesic activity. Such isosteric replacement of the phenyl ring yielded compound **48**, which exhibited high analgesic potency of short duration of action, unusually rapid recovery of motor coordination following high doses, and minimal cardiorespiratory effects as compared with opioids currently in clinical use. Such analgesics could be of great utility to clinicians for outpatient surgical procedures, patient-controlled analgesia, and computer assisted continuous infusion pain control techniques.

Experimental Section

Melting points were recorded on a Thomas-Hoover melting point apparatus and are uncorrected. ^1H NMR spectra were obtained in deuterated chloroform on a Varian EM 360 (60 MHz) or JEOL GSX 270 (270-MHz) spectrometer. Chemical shifts are reported in delta units (δ) downfield from the internal standard, tetramethylsilane. IR spectra were recorded on a Perkin-Elmer 197 spectrophotometer. Flash chromatography[24] was performed on 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. Elemental analyses (C, H, and N) were obtained from the Analytical Services Division, BOC Technical Center, Murray Hill, NJ and were within 0.4% of the theoretical values. All experiments involving organolithium reagents were carried out under an atmosphere of dry argon. Dry tetrahydrofuran, chloroform, and organolithium reagents were purchased from Aldrich, Milwaukee, WI in Sure/Seal bottles and transferred by syringe under argon. Most commercially available starting materials did not require further purification. Propionyl chloride was freshly distilled from calcium hydride prior to use. The synthesis of intermediate heteroarylethyl chlorides, 2-[2-

(24) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* 1978, *43*, 2923.

(methylsulfonyl)ethyl]thiophene,[25] and 2-methyl-5-nitro-1-(2-chloroethyl)-1*H*-imidazole[26] has been previously described. 3-(2-Tosylethyl)thiophene,[27] 2-(2-chloroethyl)pyridine hydrochloride,[28] 1-(2-chloroethyl)-1,3-benzoxazolin-2-one,[29] 4-methyl-5-(2-chloroethyl)thiazole hydrochloride,[30] 1-(2-chloroethyl)-4-iodopyrazole,[31] and 1-(2-chloroethyl)-3,5-dimethylpyrazole[32] were supplied by Dr. Jerry Bagley, Anaquest.

I. 4-Phenyl-4-anilidopiperidines. The procedures described are representative of those depicted in Scheme I.

1-Benzyl-4-phenyl-4-(2-fluoroanilino)piperidine (7b). A mixture of 1-benzyl-4-piperidone (56.18 g, 296 mmol), 2-fluoroaniline (34.33 g, 309 mmol), several crystals of p-toluenesulfonic acid (0.5 g), and toluene (250 mL) was heated at reflux for 18 h to collect the theoretical quantity of water (5.3 mL) in a Dean–Stark trap. Approximately 150 mL of toluene were distilled off by repeatedly draining the Dean–Stark trap and the reaction was cooled to room temperature under argon to give the desired imine **5b** as a thick orange syrup (IR 1660 cm^{-1}) in toluene. This viscous solution was slowly transferred under argon via a wide-bore cannula to a cold (0 °C), stirring solution of phenyllithium (600 mmol) in 7:3 cyclohexane/ethyl ether (300 mL). The reaction was stirred for 0.5 h at 0 °C, followed by 1.5 h at room temperature. The reaction mixture was then cooled and water (200 mL) was carefully added dropwise. The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo to give the crude desired diamine as a brown oil. Flash chromatography eluting with ethyl acetate/hexane (1:10) gave pure diamine **7b** as a pale yellow glass (61.92 g, 58%). An analytical sample was crystallized from hot hexane: mp 101–102 °C; ^1H NMR ($CDCl_3$) δ 2.10–2.86 (complex, 8 H), 3.55 (s, 2 H), 4.53 (d, J = 4.5 Hz, 1 H), 6.10–7.56 (complex, 14 H); IR 3400 cm^{-1}. Anal. ($C_{24}H_{25}N_2F$) C, H, N.

1-Benzyl-4-phenyl-4-[*N*-(2-fluorophenyl)propionamido]piperidine (8b). Excess propionyl chloride (100 ml, 1.15 mol) was added dropwise to a chloroform solution of **7b** (40.95 g, 113.6 mmol) at room temperature. A thick precipitate formed and the pasty reaction mixture was vigorously stirred and heated at reflux for 15 days, while the slow disappearance of the starting amine was monitored by TLC. The resultant clear amber reaction mixture was cooled and added dropwise to cold (0 °C), stirring 10% aqueous NaOH. The bilayer solution was stirred for 1.5 h and the organic layer was separated, dried (Na_2SO_4), and concentrated to give an oil. Flash chromatography eluting with ethyl acetate/hexane (1:2) afforded pure amide **8b** as an amber glass (44.47 g, 94%): ^1H NMR ($CDCl_3$) δ 0.82 (t, J = 7 Hz, 3 H), 1.71 (q, J = 7 Hz, 2 H), 2.00–3.30 (complex, 8 H), 3.30 (s, 2 H) 6.90–7.85 (m, 14 H). An analytical sample was crystallized as an oxalate salt: mp 231–233 °C. Anal. ($C_{29}H_{31}N_2FO_5$) C, H, N.

4-Phenyl-4-[*N*-(2-fluorophenyl)propionamido]piperidine (9b). 1-Chloroethyl chloroformate[7] (12 g, 83.9) was added to a cold (0 °C) solution of **8b** (29.7 g, 71.3 mmol) in 1,2-dichloroethane (400 mL). After 15 min, the reaction mixture was heated to reflux. After 2 h, the majority of the solvent was removed in vacuo and the residue was redissolved in methanol and heated at reflux for 4 h. The reaction mixture was cooled and concentrated in vacuo and the residue was dissolved in 0.5 N HCl (750 mL). After washing with ethyl ether (2 × 300 mL), the aqueous solution was basified with 25% aqueous NaOH and extracted with chloroform. The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo to give **9b** as a pale yellow oil (18.62 g, 80%), which was used without further purification.

1-[2-(4-ethyl-4,5-dihydro-5-oxo-1*H*-tetrazol-1-yl)ethyl]-4-phenyl-4-[*N*-(2-fluorophenyl)propionamido]piperidine (20). 1-(2-Bromoethyl)-4-ethyl-1,4-dihydro-5*H*-tetrazol-5-one[33] (0.9 g, 4.1 mmol) was added to a stirring solution of **9b** (1.2 g, 3.3 mmol) and powdered anhydrous K_2CO_3 (3 g) in acetonitrile (50 mL). After 2 days at reflux, the reaction mixture was cooled and filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography with ethyl acetate/hexane (2:1) to give **20** as a light brown oil (1.11 g, 72%). The oil was crystallized from hot *tert*-butyl methyl ether to give a tan solid: mp 103–104 °C; ^1H NMR ($CDCl_3$) δ 0.85 (t, 3 H), 1.40 (t, 3 H), 1.70–3.30 (complex, 12 H), 3.95 (m, 4 H), 7.15–7.70 (m, 9 H). An analytical sample was crystallized as an oxalate salt from methanol/*tert*-butyl methyl ether: mp 200 °C. Anal. ($C_{27}H_{33}N_6FO_6$) C, H, N.

II. 4-Heteroaryl-4-anilidopiperidines. The procedures described are representative of those depicted in Scheme I.

1-Benzyl-4-(4-methylthiazol-2-yl)-4-(*N*-phenylpropionamido)piperidine (8f). Excess propionyl chloride (32 g, 346 mmol) was added to a solution of 1-benzyl-4-(4-methylthiazol-2-yl)-4-anilinopiperidine[11] (**7f**, 20.38 g, 56 mmol) in $CHCl_3$ (200 mL). The reaction mixture was heated at reflux for 18 h, cooled, and stirred with 20% aqueous NaOH (300 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated to give a brown oil. Flash chromatography with ethyl acetate/hexane (1:1) afforded amide **8f** as an amber oil (21.39 g, 91%): ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7 Hz, 3 H), 1.80 (q, J = 7 Hz, 2 H), 2.05–2.35 (complex, 4 H), 2.44 (s, 3 H), 2.65 (m, 4 H), 3.40 (s, 2 H), 6.84 (s, 1 H), 7.20–7.45 (complex, 10 H). An analytical sample was crystallized as an oxalate salt: mp 216–217 °C. Anal. ($C_{27}H_{31}N_3O_5S$) C, H, N.

4-(4-Methylthiazol-2-yl)-4-(*N*-phenylpropionamido)piperidine (9f). 1-Chloroethyl chloroformate[7] (3.53 g, 24.7 mmol) was added to a cold (0 °C) solution of **8f** (9.78 g, 22.35 mmol) in 1,2-dichloroethane (250 mL). After 15 min, the reaction mixture was heated to reflux. After 2 h, the majority of solvent was removed in vacuo and the residue was redissolved in methanol and heated at reflux for 4 h. The reaction mixture was cooled and concentrated in vacuo and the residue was dissolved in 0.5 N HCl (400 mL). After washing with ethyl ether (2 × 200 mL), the aqueous solution was basified with 25% aqueous NaOH and extracted with chloroform. The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo to give **9f** as a pale yellow oil (7.48 g, 96%), which was used without further purification.

1-[2-(1*H*-pyrazol-1-yl)ethyl]-4-(4-methylthiazol-2-yl)-4-(*N*-phenylpropionamido)piperidine (48). 1-[2-(Tosyloxy)-ethyl]pyrazole[34] (1.2 g, 4.5 mmol) was added to a stirring solution of **9f** (1.06 g, 3.2 mmol) and powdered anhydrous K_2CO_3 (5 g) in acetonitrile (50 mL). After 18 h at reflux, the reaction mixture was cooled and filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography with 5% methanol/ethyl acetate to give **48** as a tan solid (1.08 g, 79%): mp 131–133 °C; ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3 H), 1.80 (q, J = 7 Hz, 2 H), 2.75 (m, 2 H), 2.35–2.75 (complex, 8 H), 2.43 (s, 3 H), 4.18 (t, J = 7 Hz, 2 H), 6.19 (s, 1 H), 6.82 (s, 1 H), 7.28–7.55 (complex, 7 H). An analytical sample was crystallized as an oxalate salt: mp 185–187 °C. Anal. ($C_{25}H_{31}N_5O_5S$) C, H, N.

Crystallography. Compound **20**, 1-[2-(4-ethyl-4,5-dihydro-5-oxo-1*H*-tetrazol-1-yl)ethyl]-4-phenyl-4-[*N*-(2-fluorophenyl)-propionamido]-piperidine, $C_{25}H_{31}N_6FO_2$, M = 466.56, was crystallized from a saturated solution in *tert*-butyl methyl ether. A clear parallelepiped with crystal dimensions 0.4 × 0.4 × 0.7 mm was selected for X-ray analysis. The crystal lattice was found to be orthorhombic, with a = 16.949 (1) Å, b = 43.782 (2) Å, c = 6.541 (1) Å, and V = 4854 (1) Å^3 (by least-squares refinement on diffractometer angles for 25 automatically centered high-angle reflections). The space group was found to be *Pnna* (#52), having Z = 8 and D_x = 1.28 g/cm^3. The absorption coefficient was

(25) Van Daele, P. G. H.; De Bruyn, M. F. L.; Boey, J. M.; Sanczuk, S.; Agten, J. T. M.; Janssen, P. A. J. *Arzneim.-Forsch. (Drug Res.)* **1976**, *26*, 1521.
(26) Alcalde, E.; Manos, L.; Elguero, J. *J. Heterocycl. Chem.* **1984**, *21*, 1647.
(27) ^1H NMR ($CDCl_3$) δ 2.35 (s, 3 H), 2.95 (t, 2 H), 4.25 (t, 3 H), 6.70–7.85 (complex, 7 H).
(28) ^1H NMR (DMSO-d_6) δ 3.65 (t, 2 H), 4.23 (t, 2 H), 7.90–8.95 (complex, 4 H).
(29) ^1H NMR ($CDCl_3$) δ 3.70 (t, 2 H), 4.21 (t, 2 H), 7.02–7.34 (m, 4 H).
(30) ^1H NMR ($CDCl_3$) δ 2.90 (s, 3 H), 3.50 (m, 2 H), 3.95 (m, 2 H), 10.25 (s, 1 H), 16.40 (br s, 1 H).
(31) ^1H NMR ($CDCl_3$) δ 3.85 (t, 2 H), 4.43 (t, 2 H), 7.57 (s, 1 H), 7.60 (s, 1 H).
(32) ^1H NMR ($CDCl_3$) δ 2.21 (s, 3 H), 2.30 (s, 3 H), 3.85 (t, 2 H), 4.25 (t, 2 H), 7.35 (s, 1 H).
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calculated to be $\mu = 7.41$ cm^{-1} at the measurement wavelength $\lambda = 1.54178$ Å. Data was collected on a Rigaku AFC5S diffractometer in the $\omega/2\theta$ mode with ω scan width = 1.470 + 0.300 tan θ, and ω scan speed 5.3–16°/min, using graphite-monochromated Cu Kα radiation. A total of 4307 reflections were measured ($0° < 2\theta < 120°$, $+h$, $+k$, $+l$), with 4192 independent reflections (merging $R = 0.004$), giving 1914 with $I > 3\sigma(I)$. Three standards were monitored every 150 reflections. No significant decay or absorption was observed. The initial atomic coordinates were obtained by direct methods and Fourier difference methods. Full-matrix least-squares refinement was carried to convergence for the position and anisotropic temperature factors of all nonhydrogen atoms. The hydrogens were assigned calculated positions, and isotropic temperature factors were 1.2 times the equivalent isotropic temperature factor of the associated nonhydrogen atom. Hydrogen parameters were updated every two refinement cycles. The weighting scheme $w = 1/[\sigma^2(F_o) + 0.000625F_o^2]$ with $\sigma(F_o)$ from counting statistics gave satisfactory agreement between F_o and F_c, with GOF = 2.06. The final R and R_w values were 0.061 and 0.086. The final difference map showed a maximum of 0.41 e/Å^3. The substituted phenyl ring is disordered between 180° rotated states. The relative occupancies of the ortho-positioned F1A and F1B were refined to 65% and 35%, respectively. Programs and computers used and sources of scattering factor data are given in ref 35.

Pharmacological Methods. Analgesic Activity. A. 55 °C Mouse Hot Plate. The hot plate assay was performed as described by Rudo et al.[36] utilizing nonfasted male mice (Swiss–Webster) weighing between 18 and 22 g. The ED_{50} and 95% confidence limits were calculated by using a standard computer program of the method of Litchfield and Wilcoxon[37] fitted to a minicomputer.[38] Calculation of the ED_{50} (95% confidence limits) was corrected for the base content of the salts.

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

C. Rat Tail Flick. A modification of the D'Armour–Smith tail-flick method[39] was employed in the evaluation of analgesic activity. Male Sprague–Dawley rats weighing between 150 and 200 g were given a thermal stimulus challenge 1 min postadministration of the test compounds in the lateral tail vein. 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.

Rat Rotarod Test for Recovery of Motor Coordination. A variation in the method first described by Kinnard and Carr[16] was used to evaluate recovery. Male Sprague–Dawley rats (Hilltop Farms, PA) about 230–290 g were housed in a temperature (70–75 °F) and humidity (50 ± 5%) controlled vivarium and allowed free access to food and water. Five rats were trained to maintain their balance for 90 s on a rotarod revolving at a constant rate of 10 rpm. The animals were allowed to rest for 5 min, and then they were retrained to the 90-s criterion. Following an additional 5 min, the ED_{100} for loss of righting (LOR) of the test drug was injected intravenously. When the animals regained their righting, they were placed on the rotarod 0, 90, and 180 s later and were tested for 90 seconds at each time interval. However, animals that remained on the rotarod for the full 90 s during any interval were not tested subsequently. The number of animals tested and meeting the 90-s criterion and their median time on the rotarod were recorded for each time interval, but only the first time interval was used for statistical comparisons. The between-drug group medians were first analyzed with the Kruskal–Wallis H statistic[23] and, if appropriate, the median rotarod durations for each group were compared to that of the alfentanil group using a Mann–Whitney U test.[23] A rotarod index (ROI) was also calculated according to the following formula: ROI = (first + second × $^2/_3$ + third × $^1/_3$)/3, where first, second, and third equal the average time on the apparatus in seconds for the respective time intervals. Animals remaining on the rotarod for the full 90 s during one interval were scored with 90 s for all subsequent intervals. Therfore, the maximum ROI attainable was (90 + 90 × $^2/_3$ + 90 × $^1/_3$)/3 = 60.

Arterial Respiratory Blood Gases in Conscious Rat. Male Sprague–Dawley rats (Hilltop Farms, PA) weighing about 300–400 g were allowed free access to food and water and housed five per cage in a temperature (72 °F) and humidity (50%) controlled vivarium with a light–dark cycle of 12 h. Prior to testing (24 h) the animals were chronically implanted with heparinized (60 units/mL) catheters in the right internal jugular vein and left common carotid artery under 2% isoflurane/100% oxygen anesthesia. The catheters were exteriorized through the nape of the neck and secured with surgical silk. 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 (Gould Electronics, Cleveland, OH). The pressure signal was displayed as systolic, diastolic, and mean blood pressure on a physiological recorder (Grass Instruments, Boston, MA). Heart rate was recorded off the pulse pressure signal and channeled through a tachograph for recording. The control values of blood pressure and heart rate were recorded for a minimum period of 15 min to insure stable base-line readings before injection of drugs. Drugs were injected through the jugular catheter, connected to a three-way stopcock via a 20-cm length of PE050 tubing filled with 0.9% saline. Injections were made slowly (10–15 s), and the injection apparatus was subsequently flushed with 0.4 mL of 0.9% saline. Arterial blood samples were taken from the carotid catheter and analyzed on a Nova blood-gas analyzer (Nova Biomedical, Waltham, MA) for pH, $paCO_2$ and paO_2. Samples were taken at 0 (i.e. control), 2, 5, 10, 15, and 20 min following injection. Cardiovascular parameters were monitored for 20 min. The onset of the drug was recorded as the time to maximum effect or minimum value. The duration of action was recorded as the time of onset to the time of return to 80% of the base-line values. Dose–response curves were constructed for respiratory depression as percent increases and decreases in the $paCO_2$ and paO_2, respectively.

Cardiovascular Function in Anesthetized, Mechanically Ventilated Rats. Male Sprague–Dawley rats weighing 300–400 g were allowed free access to food and water in a temperature (72 °F) and humidity (50%) controlled vivarium with a light–dark cycle of 12 h. Anesthesia was induced for 1 min 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 a cannula (PE-240) was inserted and tied off. Anesthesia was reduced and maintained at 2.0% (1.5 minimum alveolar concentration, MAC). Respiration was maintained through a ventilator connected to the tracheal cannula. Rate was monitored between 65 and 70 strokes per minute, volume was adjusted between 2.5 and 3.0 mL. A 21-gauge needle-tipped catheter connected to a pCO_2 monitor (Puritan Bennett) was placed in the tracheal cannula to continuously monitor the CO_2 level at approximately 30 mmHg. A Gould P-50 pressure 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. Two braided strands of aluminum wire were threaded subcutaneously around the limbs (right arm, left arm, and left leg) for electrocardiograph (ECG) recordings. The pressure signal was displayed as systolic, diastolic, and mean arterial pressure on a physiological recorder (Grass). Heart rate was recorded off the pulse pressure signal and channeled through a tachograph for recording. Three standard limb leads were connected to the subcutaneous electrodes for ECG recording through a 7P4G Grass preamplifier. The control values of blood pressure and heart rate were recorded for a minimum period of 15 min to insure stable base-line recordings before drugs were injected. Drugs were injected into the femoral vein through the exteriorized venous

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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 the injection apparatus was subsequently flushed with 0.4 mL of 0.9% saline. The above measurements were made continuously except for monitoring the isoflurane concentration via the anesthetic agent monitor (Puritan-Bennett).

Acknowledgment. We thank Aaron Carter and Greg Haynes (mouse hot plate) of the University of Maryland and Sarah Harris and Elina Messineo (rat hot plate and tail flick) of Anaquest. We are also thankful for the valuable discussions during manuscript preparation and for the chemical intermediates provided by Dr. Jerome R. Bagley.

Registry No. **5a**, 1155-57-3; **5b**, 120656-71-5; **5c**, 122822-94-0; **6a**, 968-86-5; **6b**, 120070-56-6; **7a**, 122822-95-1; **7b**, 120656-72-6; **7c**, 122822-96-2; **7d**, 120517-22-8; **7e**, 120517-23-9; **7f**, 120115-93-7; **7g**, 120517-24-0; **7h**, 120517-25-1; **7i**, 120517-26-2; **7j**, 120517-29-5; **7k**, 120517-30-8; 7l, 122823-29-4; 7m, 122823-30-7; **8a**, 122822-97-3; **8b**, 120656-73-7; **8c**, 122823-20-5; **8c**, 122823-25-0; **8e**, 122823-26-1; **8f**, 120070-49-7; **8f** oxalate, 122823-27-2; **8g**, 122823-28-3; **8h**, 122823-31-8; **8i**, 122823-32-9; **8j**, 121879-86-5; **8k**, 122823-33-0; **9a**, 122823-21-6; **9b**, 122823-22-7; **9c**, 122823-23-8; **9d**, 122823-34-1; **9e**, 122823-35-2; **9f**, 120115-94-8; **9g**, 122823-36-3; **9h**, 122823-37-4; **9i**, 122823-38-5; **9j**, 121879-87-6; **9k**, 122823-39-6; **13**, 120448-97-7; **13** oxalate, 122822-98-4; **14**, 120656-89-5; **14** oxalate, 122822-99-5; **15**, 120657-01-4; **15** oxalate, 122823-00-1; **16**, 120656-91-9; **16** oxalate, 122823-01-2; **17**, 120657-03-6; **17** oxalate, 122823-02-3; **18**, 122823-03-4; **18** oxalate, 122823-04-5; **19**, 120657-07-0; **19** oxalate, 122823-05-6; **20**, 120656-74-8; **20** oxalate, 122823-06-7; **21**, 120656-81-7; **21** oxalate, 122823-07-8; **22**, 122823-08-9; **22** oxalate, 122823-09-0; **23**, 122823-10-3; **23** oxalate, 122823-11-4; **24**, 120657-09-2; **24** oxalate, 122823-12-5; **25**, 120656-96-4; **25** oxalate, 122823-13-6; **26**, 120656-98-6; **26** oxalate, 122823-14-7; **27**, 120657-11-6; **27** oxalate, 122823-15-8; **28**, 122823-18-1; **28** oxalate, 122844-67-1; **29**, 122823-19-2; **29** oxalate, 122844-68-2; **30**, 121879-88-7; **30** oxalate, 121879-89-8; **31**, 121879-90-1; **31** oxalate, 121879-91-2; **32**, 121879-92-3; **32** oxalate, 121879-93-4; **33**, 121879-94-5; **33** oxalate, 121879-95-6; **34**, 121879-98-9; **34** oxalate, 121879-99-0; **35**, 121879-96-7; **35** oxide, 121879-97-8; **36**, 120072-10-8; **36** oxalate, 120072-11-9; **37**, 120072-12-0; **37** oxalate, 120072-13-1; **38**, 120072-14-2; **38** oxalate, 120072-15-3; **39**, 120072-16-4; **39** oxalate, 120072-17-5; **40**, 120070-50-0; **40** oxalate, 120152-15-0; **41**, 122823-16-9; **41** oxalate, 122823-17-0; **42**, 120072-24-4; **42** oxalate, 120072-25-5; **43**, 120072-06-2; **43** oxalate, 120072-07-3; **44**, 120072-26-6; **44** oxalate, 120072-27-7; **45**, 120072-08-4; **45** oxalate, 120072-09-5; **46**, 120071-99-0; **46** oxalate, 120072-00-6; **47**, 120072-01-7; **47** oxalate, 120072-02-8; **48**, 120070-51-1; **48** oxalate, 120072-03-9; **49**, 120072-04-0; **49** oxalate, 120072-05-1; **50**, 120072-28-8; **50** oxalate, 120072-29-9; **51**, 120072-18-6; **51** oxalate, 120072-19-7; **52**, 120072-20-0; **52** oxalate, 120072-21-1; **53**, 120072-22-2; **53** oxalate, 120072-23-3; *o*-$FC_6H_4NH_2$, 348-54-9; $PhNH_2$, 62-53-3; *o*-$ClC_6H_4NH_2$, 95-51-2; $PhCH_2CH_2Br$, 103-63-9; 1-(2-bromoethyl)-4-ethyltetrazol-5-one, 84501-67-7; 2-thiazolyllithium, 40610-14-8; 2-lithio-4-methylthiazole, 89602-38-0; 2-lithio-4,5-dimethylthiazole, 122823-24-9; 2-pyridinyllithium, 17624-36-1; 2-furanyllithium, 2786-02-9; 2-thienyllithium, 2786-07-4; 2-(2-bromoethyl)thiophene, 26478-16-0; 3-(2-bromoethyl)thiophene, 57070-76-5; 1-(2-bromoethyl)pyrazole, 119291-22-4; 2-(2-bromoethyl)pyridine, 39232-04-7; 3-(2-bromoethyl)-2,3-dihydrobenzoxal-2-one, 27170-93-0; 2-(2-bromoethyl)-3-methylthiazole, 671-24-9; 1-(2-bromoethyl)-2-methyl-5-nitro-1*H*-imidazole, 6058-57-7; 1-(2-bromoethyl)-4-iodopyrazole, 122823-40-9; 1-(2-bromoethyl)-3,5-dimethylpyrazole, 67000-35-5; 1-[2-(tosyloxy)ethyl]pyrazole, 80200-20-0; 1-benzyl-4-piperidone.

Supplementary Material Available: Tables listing the final atomic positional parameters, atomic thermal parameters, and bond distances and angles of compound **20**, $C_{25}H_{31}N_6FO_2$ (11 pages). Ordering information is given on any masthead page.

Selective Elimination of Interactions: A Method for Assessing Thermodynamic Contributions to Ligand Binding with Application to Rhinovirus Antivirals

Wan F. Lau and B. Montgomery Pettitt*,†

Department of Chemistry, University of Houston, Houston, Texas 77204-5641. *Received January 5, 1989*

A new method for evaluating the free energy of various physical interactions, such as hydrogen-bond, electrostatic, or van der Waals interactions, is presented. Rather than destroying or creating whole groups, selective (pairwise) interactions are eliminated from the total potential energy and the energy difference with the fully interacting system is evaluated. The exponential ensemble average of such an energy difference is then directly related to the corresponding free energy difference. This procedure is then applied to a rather large protein–ligand system involving the coat proteins of a human rhinovirus and an antiviral ligand. The results seem to indicate that a particular bent hydrogen bond between the ligand and protein system may not be favorable for binding. The method presented gives an estimate of the hydrogen bond free energy contribution with an available trajectory that was previously computed without the expenditure of sizeable computational resources such as recomputing a trajectory. This procedure is effective and efficient for computing the free energy for a given type of physical interaction. It can be used for calculating the binding energy differences for various interactions which can be used to guide the search for isosoluble synthetic targets.

I. Introduction

Many interactions may contribute to the binding of a ligand to a macromolecule. These include electrostatic, van der Waals (dispersion) and, often, hydrogen-bond interactions. Of these various interactions, the requirements for satisfying the potential hydrogen bonds between the protein and its ligand are frequently considered to be among the most important in designing new analogous ligands. If a ligand forms favorable hydrogen bonds with a solvent, and is thereby soluble, it is often reasonable to assume that for a favorable free energy change upon binding there will have to be a compensating number of similar interactions at the binding site. Otherwise, it seems that the equilibrium for binding would be driven in an unfavorable direction. In this work we present a seemingly counterintuitive example where the scenario just mentioned apparently does not hold, when viewed in its simplest form, because the hydrogen bond in question is bent, thereby causing unfavorable interactions with the antecedent atoms involved in the hydrogen bond.

We have earlier attempted to calculate the difference in the free energy of binding between the antiviral WIN52084 and a desmethyl analogue to the coat proteins

† Alfred P. Sloan Fellow 1989–1991.

0022-2623/89/1832-2542$01.50/0