Antinociceptive (Aminoalkyl)indoles

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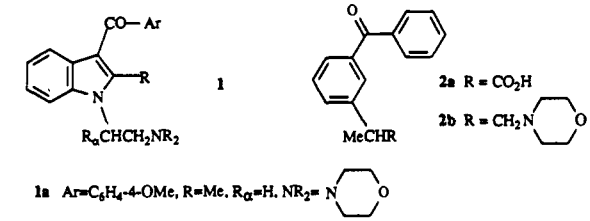
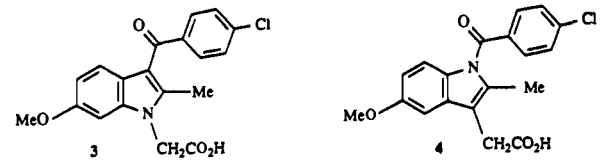
The (aminoalkyl)indole (AAI) derivative pravadoline (**1a**) inhibited prostaglandin (PG) synthesis in mouse brain microsomes in vitro and ex vivo and exhibited antinociceptive activity in several rodent assays. In vitro structure–activity relationship studies of this new class of PG synthesis inhibitors revealed a correspondence in three respects to those reported for the arylacetic acids: (1) "α-methylation" caused an increase in PG inhibitory potency, (2) the (*R*)-α-methyl isomer was more active than the S isomer, (3) the hypothesized aroyl group conformation of the 2-methyl derivatives corresponded to the proposed and reported "active" conformations of the aroyl and related aromatic acetic acid derivatives. The ^{1}H NMR chemical shift of the C-4 hydrogen of pravadoline in comparison to the deshielding seen with **50**, which lacks a substituent at C-2, suggested that the carbonyl group of pravadoline is located near C-2 but is located near C-4 in **50**. Associated with this conformational change of the carbonyl group of **1a** is a diminution of PG synthetase inhibitory activity. The results of UV and difference nuclear Overhauser studies of the two compounds were consistent with these conformational assignments. The low eudismic ratios of the α-methyl derivatives and the observation that the side chain may be extended by three methylene groups without significant loss of PG inhibitory potency suggests that this class of inhibitors bound less strongly and less selectively to the active site of PG synthetase than do the arylacetic acids. Two AAIs, **1a** and **30**, were found to be metabolized to the corresponding acetic acid derivatives, both of which inhibited PG synthesis. An exception to the observation that the antinociceptive activity of the AAIs was associated with PG synthetase inhibitory activity was the 1-naphthoyl derivative **67** since neither it nor its acetic acid metabolite **74** inhibited PG synthesis. Yet **67** was antinociceptive in four different rodent assays. This naphthoyl derivative, like opioids, also inhibited electrically stimulated contractions in the mouse vas deferens (MVD) preparation. Unlike opioids, however, the inhibition was not antagonized by naloxone. A subseries of AAIs was identified, of which **67** was prototypic. These compounds lacked PG synthetase inhibitory activity, but their inhibitory potency in MVD preparations correlated roughly with their antinociceptive potency in vivo. Pravadoline was also inhibitory in the MVD. Its antinociceptive activity, therefore, may be a consequence of both its PG synthetase inhibitory potency and another antinociceptive mechanism, the latter associated with its inhibitory potency in the MVD. The evidence is summarized which suggests that this second antinociceptive mechanism is associated with binding to the recently characterized cannabinoid receptor.

Introduction

Despite the enormous effort devoted to the investigation of structural variations of the class of drugs broadly known as NSAIDs, no drug entity has emerged that is widely accepted as possessing significantly improved efficacy or even a diminished side effect potential. The medicinal chemical literature of this drug class is summarized in a review.[1] The best known NSAID structural types are acidic in nature and assignable to three major categories: the arylacetic acids, the fenamic acids, and the oxicam structural types. They are inhibitors of prostaglandin (PG) synthesis, and most of them have been shown or are believed to be inhibitors of the enzyme complex cyclooxygenase (CO). It is also true that most of the synthetic effort has focused on variation of the aromatic nucleus which invariably accompanies the acidic functional group.

In this report we introduce a new type of compound of general structure **1** related, as will be seen, to the classical NSAID structures but where the acidic functional group is replaced by an aminoalkyl group. These (aminoalkyl)indole (AAI) structures, particularly the morpholine derivatives, have structural precedent. Schlegel, Zenitz, and co-workers[2] reported a series of amine analogues **2b** of the well-known NSAID ketoprofen (**2a**). These compounds are claimed to be less ulcerogenic than several NSAIDs. One member of the series was shown to be a PG synthetase inhibitor in vitro. The AAIs are also close relatives of the analgesic drug clometacin **3**,[3,4] which is an isomer of the antiinflammatory drug indomethacin (**4**). The activity of both drugs is believed to be a consequence of the inhibition of PG synthesis.





Chemistry

Most of the compounds utilized in these studies were prepared by established procedures; they are summarized in Scheme I. In path a, the C-3 aroyl group was introduced in the first step to give **5** followed by N-1 alkylation to afford the target **7**. In path b, N-alkylation afforded **6**, which was acylated at C-3 to give the desired **7**. Additional transformations were employed to synthesize variations of the aminoalkyl side chains. For example, displacement of the tosylate residue in **7a** with a variety

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(1) *Nonsteroidal Antiinflammatory Drugs*; Lombardino, J. G., Ed.; John Wiley and Sons: New York, 1985.

(2) Schlegel, D. C.; Zenitz, B. L.; Fellows, C. A.; Laskowski, S. C.; Behn, D. C.; Phillips, D. K.; Botton, I.; Speight, P. T. *J. Med. Chem.* 1984, *27*, 1682.

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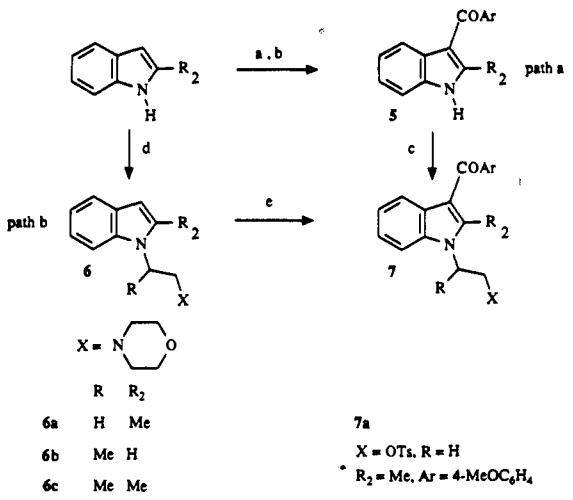
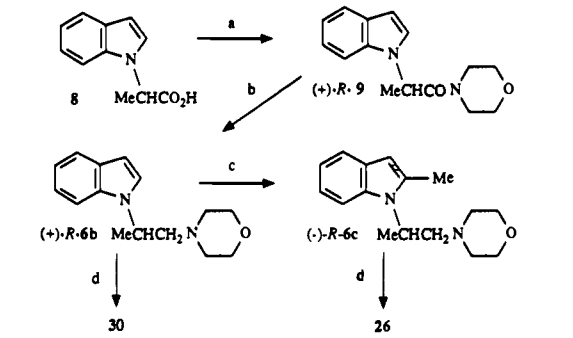
Scheme I[a]



[a] (a) MeMgBr, CH_2Cl_2, Et_2O; (b) ArCOCl; (c) $ClCH_2CH_2NR_3R_4$, K_2CO_3, DMF; (d) $ClCH_2CH_2$-4-morpholinyl, KOH, DMSO; (e) ArCOCl, $AlCl_3$.

Scheme II[a]



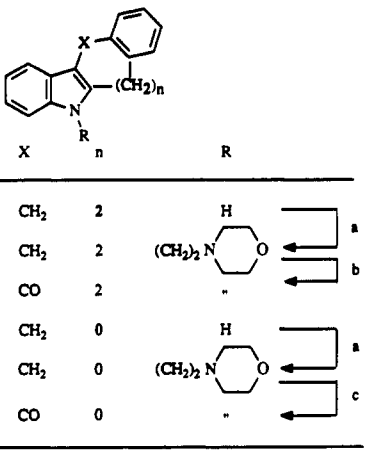
[a] (a) Me_3CCOCl, Et_3N, morpholine; (b) Vitride, C_6H_5Me; (c) 1. n-BuLi, Et_2O; 2. MeI; (d) $AlCl_3$, 2-F-C_6H_4COCl.

of amines served as a general procedure to prepare variations of the amine group.

A subseries of analogues included the α-methyl derivatives, such as **25** and **29**. Their precursors resulted from alkylation of indole or 2-methylindole with α-bromomorpholinopropanamide and subsequent amide reduction with LAH or Vitride to give **6b** and **6c**. The enantiomers **26**, **27**, **30**, and **31** were obtained by resolution of **6b** or **6c**, as their dibenzoyltartaric acid salts, followed by acylation of the resolved intermediate. A chiral synthesis was subsequently developed that provided chemical correlation of absolute configuration (Scheme II). (*R*)-Indole-2-propionic acid (**8**), obtained by alkylation of indole with the chiral synthon (*S*)-2-bromopropionic acid,[5] was converted to the amide (+)-*R*-**9** without racemization. Vitride reduction gave (+)-*R*-**6b** and Friedel–Crafts acylation afforded (−)-(*R*)-**30**. Correlation of configuration in the optically pure 2-H-/2-CH_3-indole pair **30** and **26** was achieved by metalation at C-2 of (+)-(*R*)-**6b** with n-BuLi followed by methylation with CH_3I to give (−)-(*R*)-**6c**.

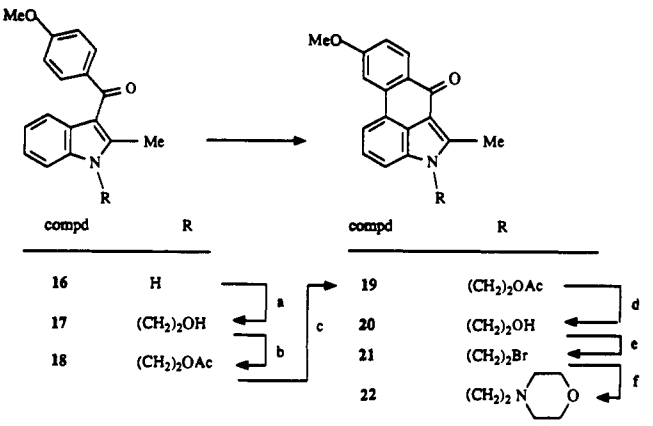
Two conformationally restrained aroyl derivatives were prepared as shown in Scheme III. For both $n = 0$ and 2, the known compounds **10**[6] and **13**[7] were N-alkylated to give

Scheme III[a]



[a] (a) NaH, DMF, $ClCH_2CH_2$-4-morpholinyl; (b) DDQ, THF, H_2O; (c) 3,5-dimethylpyrazole, THF, NaH, O_2 (ref 8).

Scheme IV[a]



[a] (a) n-BuLi, THF, ethylene oxide; (b) Ac_2O, KOAc, C_6H_5Me; (c) $Pd(OAc)_2$, AcOH; (d) K_2CO_3, MeOH, CH_2Cl_2; (e) CDI, MeCN, allyl bromide; (f) morpholine, DMF.

Table I. Inhibition of PG Synthesis in Mouse Brain Microsomes in Vitro: Comparison of Pravadoline and Reference Standards[a]

compd	IC_{50}, μm
pravadoline	3.5 (1.4–8.6)[b]
naproxen	13 (1.5–30)
indomethacin	0.5 (0.4–0.7)
clometacin	0.2 (0.07–0.54)
ibuprofen	13 (7.8–20)

[a] See ref 12 for experimental procedures. [b] 95% confidence limits.

11 and **14**. Subsequent oxidation provided **12** and **15**.

The synthesis of another restrained aroyl compound **22** is described in Scheme IV. This compound has the aroyl phenyl ring of pravadoline directly attached to the indole nucleus at C-4. Initial attempts at direct thermal intramolecular oxidative coupling of **1a** as the free base, its corresponding hydrochloride salt, or its *N*-oxide using palladium(II) salts[9] were unsuccessful. Palladium-mediated cyclization of the 2-hydroxyethyl derivative **17** led to a 5% yield of cyclized product, isolated as the acetate derivative **19**. Direct cyclization of acetate **18** resulted in

(3) Allais, A.; Meier, J.; Mathieu, J.; Nomine, G.; Peterfalvi, M.; Deraedt, R.; Chifflot, L.; Benzoni, J.; Fournex, R. *Eur. J. Med. Chem.* **1975**, *10*, 187.
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(6) Muth, C. W.; Steiniger, D. O.; Papanastassiou, Z. B. *J. Am. Chem. Soc.* **1955**, *77*, 1066.
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(9) Ithara, T.; Sakakibara, T. *Synthesis* **1978**, 607.

Table II. Potency of Pravadoline (1a) and 67 in Antinociceptive Tests[a]

test	ED_{50}, mg/kg po	
	1a	67
acetylcholine (ACh) writhing (mouse)	41 (26–61)[c]	97 (54–172)
		0.19 (0.12–0.32) iv
acetic acid writhing (rat)	15 (5–44)	38 (24–59)
intraarterial bradykinin (rat)	120 (73–180)	52 (45–60)
adjuvant arthritis paw flexion (rat)	100 (99–101)	30
Randall-Selitto (rat)	1[d]	...

[a] Reference 12 should be consulted for details of test procedures and comparison with reference standards. [b] The vehicle was gum tragacanth or acidified water or acidified dextrose. [c] 95% confidence limits. [d] Minimum effective dose.

a 3-fold improvement in the yield of **19**. Hydrolysis of **19** to **20** and conversion to the bromide **21** (carbonyldiimidazole, allyl bromide, CH_3CN)[10] set the stage for the transformation to the conformationally restricted target **22** using standard conditions.

Results and Discussion

The PG synthetase inhibitory potencies of pravadoline[11] (**1a**), a leading member of the series, and several reference standards are presented in Table I. Mouse brain microsomes were used as a representative tissue from a species in which antinociceptive screening was conducted. Haubrich and co-workers[12] have reported that pravadoline and several reference PG synthetase inhibitors block the postmortem rise in mouse brain PG content. A comparison of their intravenous inhibitory potencies in this test with their antinociceptive potencies in the acetylcholine (ACh) writhing test suggested that the observed antinociceptive activity is associated with PG synthetase inhibitory activity.[13] The PG synthetase inhibitory activity reported here was measured by determining the inhibition of conversion of radiolabeled arachidonic acid to PGE_2. Several members of the series have been tested as PG synthetase inhibitors in the more commonly used bovine seminal vesicle tissue and have been found to have approximately the same inhibitory potency as seen in mouse brain microsomes.

The oral acetylcholine writhing test served as the initial assay for the evaluation of the antinociceptive activity in vivo. The activity of pravadoline in this test and four other antinociceptive assays is presented in Table II. The observation of in vitro PG synthetase inhibitory and in vivo acetylcholine writhing inhibitory activity for the AAIs is consistent with but, of course, does not prove that the in vivo activity is a consequence of PG synthetase inhibitory activity.

To determine the extent to which the structure–activity relationship (SAR) of this new series resembled that of the arylacetic acids, we examined the "α-methyl" morpholinoethyl derivatives **23** and **25**. "α-Methylation" of an arylacetic acid to form a 2-arylpropionic acid normally results in an increase in PG synthetase inhibition, and the PG synthetase inhibitory activity of the arylpropionic acids is a property associated largely with the corresponding *S*

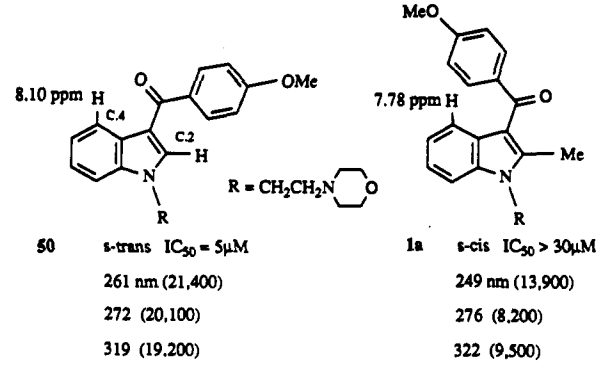


Figure 1. Proposed conformations of **50** and **1a**. NMR spectra were determined in $CDCl_3$ with TMS as the internal standard. UV spectra were measured in 95% EtOH.

isomer.[1,14] The α-methyl compounds **23** and **25** were respectively 4 and 18 times more potent in inhibiting PG formation in vitro than their unmethylated counterparts, **1a** and **24**. The *R* enantiomers **26** and **30** were about 10 times more active than the corresponding *S* enantiomers **27** and **31**. It should be noted that the *R* configuration in the morpholinoethyl series corresponds spatially to the same absolute configuration as the *S* isomer for the traditional NSAID carboxylic acids, a consequence of nomenclature rules. The stereoselectivity for the "α-methyl" derivatives of the morpholinoethyl compounds thus corresponds to that reported for the known carboxylic acids despite the contrasting nature of the functional groups.

The (*R*)-carboxylic acid **36** was 19 times more active than the *S* isomer **35**. The eudismic ratio is not significantly different from those observed for the two morpholine pairs discussed above. This observation is not consistent with Pfeiffer's rule, which states that the greater the activity of a racemate, the greater the eudismic ratio of the corresponding enantiomers.[15]

The correspondence in SAR between the AAIs and the arylacetic acids at the "α" carbon is consistent with the concept that the AAIs and the arylacetic acids bind to the same site. The lower eudismic ratios observed for the AAIs suggest, however, that the AAIs bind less strongly to the asymmetric site than do the arylacetic acids. The observation that the amine group may be separated from the indole nitrogen atom by four to six carbon atoms (**47–49**) with retention of significant PG synthetase inhibitory activity further supports the view that the aminoalkyl group binds to the enzyme in a nonspecific fashion. Modification of the amino group located two carbons from the indole nitrogen can, nevertheless, result in significant changes in potency (**37–46**). This observation is consistent with the idea that binding interactions are available to the amines which are not available to the carboxylic acids. Alternatively, these effects could be a simple consequence of variations in the pK_a of the amine which is reflected in its extent of ionization at physiological pH.

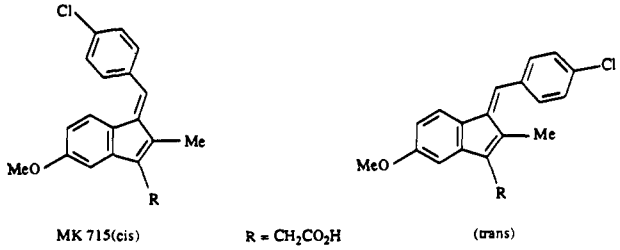
Alteration of the size of the group at C-2 affects the conformational status of the aroyl group at C-3, a change that paralleled a consistent effect on PG synthetase inhibitory activity. The comparative inhibitory activity of the 2-Me/2-H pairs **1a/50**, **24/28**, and **25/29** as well as their corresponding enantiomers is illustrative. The change 2-Me to 2-H on the indole ring invariably resulted in a reduction of PG synthetase inhibitory activity. Accompanying this change is a difference in chemical shift of the

(10) Kamijo, T.; Harada, H.; Iizuka, K. *Chem. Pharm. Bull.* **1983**, *31*, 4189.
(11) Pravadoline is the USAN approved name for **1a**.
(12) Haubrich, D. R.; Ward, S. J.; Baizman, E.; Bell, M. R.; Ferrari, R.; Bradford, J.; Miller, M.; Perrone, M.; Pierson, A. K.; Saelens, J. K.; Luttinger, D. *J. Pharmacol. Exp. Ther.*, in press.
(13) Ferrari, R. A.; Ward, S. J.; Zobre, C. M.; Kiefer, D.; Perrone, M. H.; Connell, M. J.; Haubrich, D. R. *Eur. J. Pharmacol.* **1990**, *179*, 25.
(14) Hutt, A. J.; Caldwell, J. *Clin. Pharmacokinet.* **1984**, *9*, 371.
(15) Lien, E. J.; Rodriguez de Miranda, J. F.; Ariens, E. J. *Mol. Pharmacol.* **1976**, *12*, 598.

indole C-4 proton in the NMR spectrum. Invariably, the 2-H analogues exhibit a downfield shift of this proton, relative to their 2-Me isomers. These data and the UV spectra are presented in Figure 1 for the **1a/50** pair. The structures are written as two-dimensional approximations of the proposed three-dimensional conformations. The deshielding seen for the C-4 hydrogen in the NMR spectrum of **50** is due to the proximity of the carbonyl group to the C-4 hydrogen (s-trans form). The normal aromatic resonance of this proton in the 2-methyl derivatives we believe to be a consequence of the carbonyl group being located near the C-2 methyl group (s-cis form). The approximate doubling of the extinction coefficients of the three principal maxima in the UV spectrum in going from **1a** to **50** can be related to the more extended chromophore of **50** compared with **1a**.[16]

Modeling studies in which the carbonyl group is rotated to a coplanar relationship with the indole ring and pointing toward either C-4 or C-2 resulted in severe steric interaction of the oxygen of the carbonyl group and either the C-4 proton or the protons of the C-2 methyl group. The conformationally fixed derivatives **12** and **15** (Scheme III) and **22** (Scheme IV) did not inhibit PG synthetase at 30 μM. These derivatives have the aroyl group linked by ring formation at C-2 and C-4 of the indole nucleus and thus represent a test of high-energy conformations that are disfavored in the open-chain form. Similarly restricted derivatives in other PG inhibitor series also lacked significant PG synthesis inhibitory activity.[17]

The proposal that the dominant conformations of the 2-H and 2-Me derivatives in solution were s-trans and s-cis, respectively, is supported by nuclear Overhauser difference studies. A 4% signal intensity enhancement was observed for the C-4 proton on the indole ring of **1a** when the ortho protons of the anisoyl group were irradiated. Irradiation of the methyl group at C-2 showed no enhancement of the anisoyl proton signals. A 12% enhancement was observed for the C-2 proton of **50** when the ortho protons of the anisoyl group were irradiated while no enhancement was observed for the C-4 proton. Irradiation of the C-2 proton resulted in a 5% enhancement of the ortho protons of the anisoyl group. Similar conformational assignments have been reported for a series of 2-substituted 3-aroylbenzofuran derivatives.[18] The pictured conformation of **1a**, the more potent PG synthetase inhibitor of the **1a/50** pair, corresponds to the proposed "active" conformation of the PG synthesis inhibitors and the cis indene, MK 715, in



MK 715(cis) R = CH_2CO_2H (trans)

which the aryl group is restrained by the geometry of the exocyclic double bond.[19] MK 715 is a member of a series of PG synthesis inhibitors. Although the in vitro enzyme inhibitory activity is not available for the portrayed cis/trans pair, MK 715 is reported to be 5 times more active than the trans isomer in the carrageenan-edema assay. In a series of known PG synthetase inhibitors, activity in this test may be considered a reflection of PG synthetase inhibitory activity.[1]

The results of an X-ray determination of the structure of **1a** as the free base showed the carbonyl pointing toward C-2 and a torsion angle between the carbonyl group and the indole ring equal to 23.5°. In contrast, the crystal structure of the maleic acid salt **1b** of **1a** shows the carbonyl group pointed toward the C-4 hydrogen atom. In this conformation the angle between the carbonyl group and the plane of the indole ring is 19°. Although both conformations appear to represent minima for **1a** in the crystal state, spectroscopic studies only detect the s-cis form in solution.

Studies of the ultraviolet spectra suggest a limit as well to the orientation of the carbonyl group with the phenyl ring. The UV spectra of three model compounds are presented in Table IV. Here it is seen that the principal chromophore is the indole-3-carbonyl system. In order to account for the UV spectra, the carbonyl group of **1a** cannot, therefore, be orthogonal to the indole ring and probably cannot be more than 60–70° out of the plane of the indole ring.[16] Addition of a phenyl group resulted in a significant auxochromic shift, an observation that supports the view that the added phenyl group is cross conjugated with and thus not too far out of the plane of the carbonyl group. The torsion angles observed in the two crystal structures were 36.5° for the free base form of **1a** and 36.2° for the maleic acid salt of **1a**.

The nature of the substituent at C-2 should also affect the conformation of the basic side chain at N-1. Nilsson[20] observed that a methyl group at C-2 of 1-isopropylindole caused an increase in the population of one of the two dominant conformers of the isopropyl group in comparison with the C-2 H derivative, but the calculated differences in the free energies of the conformers was small. The corresponding effects may well occur with the α-methyl AAIs, but the required low-temperature NMR studies have not been carried out to examine that possibility.

Examples of compounds in which the substitution pattern of the aroyl group is varied are shown in Table III (**52–65**). The 3′- and 2′-OMe (**52** and **53**) analogues of **1a** are inactive at 30 μM as inhibitors of PG synthetase yet the 2′-fluoro (**24**) and 4′-F (**56**) are both active and the 3′-F derivative **57** is inactive. There is no obvious explanation for these results. Among the 4′-substituted derivatives the activity of the MeS (**64**) and MeSO (**65**) derivatives is noteworthy. Both compounds are active in vivo but only the MeS derivative is active in vitro. The sulfoxide may be a prodrug for the sulfide as is the case with the PG synthetase inhibitor sulindac.[21]

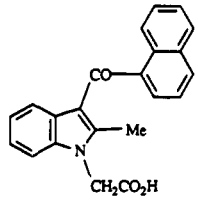
The relationship of the in vivo test results to the in vitro PG inhibitory activity of the AAIs was confounded by the metabolism of this class of compounds. **1a** and **30**, for example, were extensively metabolized in the mouse to the corresponding carboxylic acid derivatives, **32** and **36**, both of which inhibited PG synthetase in vitro. Nevertheless, despite the metabolism to arylacetic acids, the results of in vivo studies of selected members of the AAI series revealed a pharmacological profile that was unique to the AAI class. The results of these investigations have been

(16) *Theory and Applications of Ultraviolet Spectroscopy*; Jaffe, H. H., Orchin, M., Eds.; John Wiley and Sons: New York, 1962; Chapter 15.
(17) Olson, D. R.; Wheeler, W. J.; Wells, J. N. *J. Med. Chem.* **1974**, *17*, 167.
(18) Deleuze, C.; Nisato, D.; Gatto, V. L.; Chatelain, P.; Gubin, J. *Magn. Reson. Chem.* **1987**, *25*, 227.
(19) Gund, P.; Shen, T. Y. *J. Med. Chem.* **1977**, *20*, 1146.
(20) Nilsson, I.; Berg, U.; Sandström, J. *Acta Chem. Scand.* **1984**, *B38*, 491.
(21) Shen, T. Y.; Winter, C. A. In *Advances in Drug Research*; Harper, N. J., Simmonds, A. B., Eds.; Academic Press Inc.: New York, 1977; Vol. 12, p 170.

reported elsewhere[12] but will be summarized here.

The possibility that pravadoline had opioid-like properties in addition to PG synthetase inhibitory activity was ruled out since it did not bind to opioid receptors and its antinociceptive activity was not antagonized by naloxone.[12,22] In the process of assessing pravadoline for opioid-like properties, however, the drug was examined in the electrically stimulated mouse vas deferens (MVD) preparation. Pravadoline, like opioids, was inhibitory in this assay, but unlike opioids its inhibitory effect was not blocked by naloxone. Furthermore, pravadoline's inhibitory effects in the MVD were not blocked by a number of known receptor antagonists and pravadoline did not bind to a number of radioligand binding sites.[22]

Parallel SAR studies resulted in the identification of a subseries of AAI derivatives that lacked PG synthetase inhibitory activity but that did exhibit antinociceptive activity in rodent assays. Representative of this group is **67** (Table V) whose antinociceptive potency in four tests is presented in Table II. The compound did not inhibit PG synthetase activity in vitro or ex vivo,[23] and its acetic acid metabolite, **74**, was not an inhibitor of PG synthetase in vitro. Compound **67** was inhibitory in the MVD preparation with an IC_{50} = 0.015 μM. By comparison pravadoline had an IC_{50} = 0.5 μM.[22]



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In an effort to correlate the observed antinociceptive properties of the AAIs with their inhibitory potency in the MVD preparation, pravadoline and three analogues (**66**, **68**, **69**) of **67** were selected that lacked CO inhibitory activity in vitro and whose IC_{50}'s in the MVD ranged from about 0.6 to 0.006 μM. As can be seen from the data presented in Table V for this limited subseries, the rank order potency in the MVD preparation correlated roughly with their iv and po potency in the ACh writhing test.

Extensive investigation into the specific site at which AAIs may interact in the MVD revealed that AAIs interact with a G-protein coupled receptor, activation of which produces an inhibition of adenylate cyclase activity.[23b,c] Further studies using a radiolabeled AAI analogue demonstrated that the AAI binding site, which is heterogeneously distributed in the brain, may be synonymous with the binding site for CP 55940, a synthetic cannabinoid.[23d,24] Cannabinoids, like AAIs, are inhibitory against adenylate cyclase, are inhibitory in the MVD, and are antinociceptive in vivo. Exploration of the SAR of AAIs for this receptor and the areas of potential overlap with previously established cannabinoid SAR will be the subject of future publications.

Experimental Section

Proton (^{1}H) NMR spectra were measured at 100 MHz on a Varian HA-100 instrument or at 200 MHz on an IBM instrument using $CDCl_3$ as solvent. NOE data were obtained on a JEOL FX-270 instrument using 0.04 M solutions in $CDCl_3$. The solutions were deoxygenated by He purge. The percent NOEs reported are based on measured peak height intensities. Carbon (^{13}C) NMR spectra were measured at 67.8 MHz on a JEOL FX-270 instrument. IR spectra were measured on a Nicolet 20 SX FT IR or on a Perkin-Elmer Model 467 instrument. UV spectra were measured on a Gilford Response UV-vis spectrophotometer. Mass spectra were measured on a JEOL JMS-01SC instrument. Elemental analyses were performed by Galbraith Laboratories of Knoxville, TN. Melting points are not corrected. All structures were consistent with NMR, IR, MS, UV, and TLC. The syntheses of **34** and its enantiomers (**35**, **36**) have been published.[5]

Analytical thin-layer chromatography (TLC) was performed on E. Merck 5 × 20 cm Kieselgel 60 F-254 plates. Column chromatography was performed with Whatman LPS2 (37–53 μM) SiO_2 or Kieselgel 60 (230–400 mesh). Gas chromatographic analysis was performed on a Varian Model 3700 instrument with a flame-ionization detector. Preparative high-pressure liquid chromatography (HPLC) was performed on a Waters Prep 500 instrument using SiO_2 cartridges. Analytical HPLC was performed on a Waters 6000A instrument using an Alltech C_{18} column (10 μ; 4.6 mm × 25 cm).

A gas chromatographic (GC) method was developed for analysis of enantiomeric purity of (+)-*R*-**9**. The column was an XE-60-S-Val-S-A-PEA, 50 m × 0.22 mm i.d., WCOT fused silica. The flow rates were as follows: nitrogen, 2.0 mL/min; air, 300 mL/min; helium, 20 mL/min; and nitrogen splitter flow, 80 mL/min. The oven temperature was 175 °C, the injection port temperature was 250 °C, and the detector temperature was 260 °C. An analytical HPLC procedure was developed for enantiomeric purity assessments of the enantiomers of **6b** and **6c**. A suitable separation of the enantiomers was achieved with use of a Pharmacia LKB Enantiopac, 4.0 × 100 mm column, with UV detection of the eluent at 280 nm. The mobile phase was H_2O/2-PrOH/0.4 M sodium phosphate buffer, pH 7.0 (91:4:5). The flow rate was 0.4 mL/min.

Analytical instrumentation for pharmacokinetic measurements included a Varian 5060 HPLC using an Alltech C_{18} column, a Varian 9090 autosampler, and a variable-wavelength detector interfaced with a Hewlett-Packard Laboratory Automation System for data acquisition and processing. The detector was set at 272 nm for **1a** and **32**, 316 nm for **30** and **34**, and 320 nm for **67** and **74**. The mobile phase for **1a** and **32** was MeOH/0.3 M NH_4OAc/AcOH (75:25:2, v/v/v); for **30** and **34** was MeOH/0.3 M NH_4OAc/AcOH (750:250:12, v/v/v) and for **67** was MeOH/H_2O/NH_4OAc (850:150:2, v/v/w). The mobile phase for **74** was MeOH/H_2O/NH_4OAc (650:350:2, v/v/w). The flow rate in each case was 1.0 mL/min.

(4-Methoxyphenyl)(2-methyl-1*H*-indol-3-yl)methanone (**16**). To a mechanically stirred solution of 215 mL (0.60 mol) of a 2.8 M solution of MeMgBr in Et_2O, diluted with 100 mL of anhydrous Et_2O, under N_2 at 0 °C was added dropwise over 45 min a solution of 65 g (0.50 mol) of 2-methylindole in 250 mL of Et_2O. The reaction mixture was allowed to warm to room temperature and then a solution of 85.3 g (0.50 mol) of *p*-anisoyl chloride in 75 mL of Et_2O was added dropwise. A thick, orange, gummy solid formed. The mixture was refluxed for 1.5 h, allowed to cool, and then quenched cautiously by the slow addition of saturated aqueous NH_4Cl. Stirring was continued until the solids present were broken up to a fine suspension. The Et_2O was removed by distillation at atmospheric pressure. After cooling,

(22) Ward, S. J.; Mastriani, D.; Casiano, F.; Arnold, R. *J. Pharmacol. Exp. Ther.*, in press.

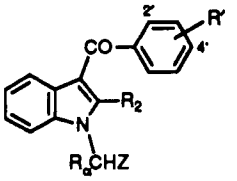
(23) (a) Ward, S. J.; Miller, M.; Luttinger, D.; Eissenstat, M. A.; Bell, M. R. *Neurosci. Abstr.* **1988**, *14*, 325. (b) Pacheco, M.; Childers, S.; Ward, S. J. *Neurosci. Abstr.* **1990**, *14*, 325. (c) Pacheco, M.; Childers, S. R.; Ward, S. J., to be published. (d) Herkenham, M.; Lynn, A. B.; Little, M. D.; Johnson, M. R.; Melvin, L. S.; de Costa, B. R.; Rice, K. C. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 1932.

(24) (a) Ward, S. J.; Baizman, E.; Bell, M.; Childers, S.; D'Ambra, T.; Eissenstat, M.; Estep, K.; Haycock, D.; Luttinger, D.; Miller, M.; Pacheco, M. *Comm. Probl. Drug Depend.*, in press. (b) Haycock, D. A.; Kuster, J. E.; Stevenson, J. I.; Ward, S. J.; D'Ambra, T. *Comm. Probl. Drug Depend.*, in press. (c) Devane, W. A.; Dysarz III, F. A.; Johnson, M. R.; Melvin, L. S.; Howlett, A. C. *Mol. Pharmacol.* **1988**, *34*, 605.

(25) Cherry, W. H.; Davies, W.; Ennis, B. C.; Porter, Q. N. *Aust. J. Chem.* **1967**, *20*, 313.

(26) Dickinson, R. P.; Iddon, B. *J. Chem. Soc. C* **1971**, 3447.

Table III. Inhibition of PG Synthetase and ACh Writhing by the AAIs[a]



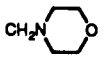
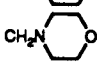
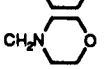
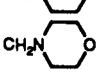
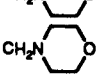
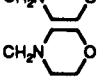
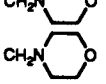
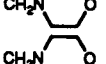
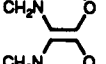
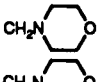
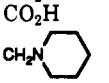
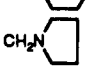
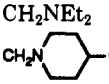
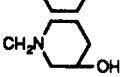
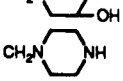
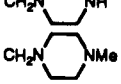
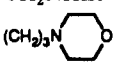
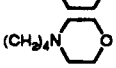
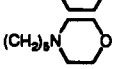
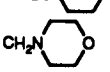
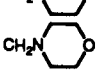
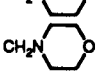
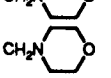
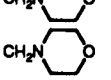
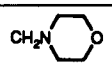
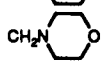
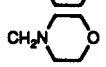
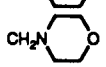
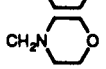
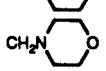
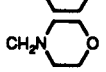
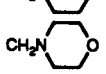
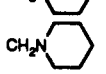
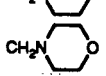
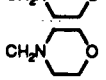
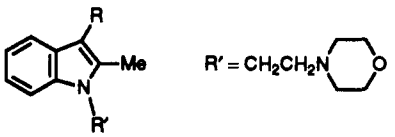
compd	Z	R′	R_α	R_2	PG synthetase inhibition in vitro: IC_{50}, μm, or inhibition at 30 μm	ACh writhing inhibition: ED_{50},[b] mg/kg po
1a		4′-OMe	H	Me	3.5 (1.4–8.6)[c]	41 (26–61)
23		4′-OMe	Me	Me	0.9 (0.4–3.2)	28 (16–54)
24		2′-F	H	Me	18 (9.9–31)	79 (49–127)
25		2′-F	Me	Me	0.7 (0.15–3.4)	19 (12–31)
26***R***		2′-F	Me	Me	0.7 (0.3–1.8)	9 (4–20)
27***S***		2′-F	Me	Me	8 (3.4–17)	37 (15–93)
28		2′-F	H	H	9%	NT[d]
29		2′-F	Me	H	12 (3.9–39)	19 (11–32)
30***R***		2′-F	Me	H	9 (4.5–19)	11 (4–29)
31***S***		2′-F	Me	H	79 (13–490)	48 (33–68)
32	CO_2H	4′-OMe	H	Me	10 (1.5–66)	173 (100–342)
33	CO_2H	2′-F	Me	Me	1.4 (0.5–3.7)	12 (6–23)
34	CO_2H	2′-F	Me	H	0.3 (0.14–0.67)	8 (3–22)
35***S***	CO_2H	2′-F	Me	H	3 (1.5–6.2)	38 (iv) (29–50)
36***R***	CO_2H	2′-F	Me	H	0.16 (0.02–0.97)	5 (iv) (3–10)
37		4′-OMe	H	Me	63%	71% at 300
38		4′-OMe	H	Me	75%	255 (158–381)
39	CH_2NEt_2	4′-OMe	H	Me	81%	50 (37–68)
40		4′-OMe	H	Me	NT	68 (42–110)
41		4′-OMe	H	Me	59% (3 μM)	26 (15–47)
42		4′-OMe	H	Me	1.4 (0.3–7)	21 (20–22)
43		4′-OMe	H	Me	NT	53 (33–85)
44	CH_2NMe_2	4′-OMe	H	Me	NT	65 (37–112)
45	CH_2NH_2	4′-OMe	H	Me	NT	42 (19–93)
46	CH_2NHEt	4′-OMe	H	Me	NT	46 (38–55)
47		4′-OMe	H	Me	86%	56 (29–107)
48		4′-OMe	H	Me	5 (3–8)	15 (8–29)
49		4′-OMe	H	Me	0.5 (0.2–1.5)	28 (18–45)
50		4′-OMe	H	H	>30 μM	73 (36–167)
51		4′-OMe	H	Et	5	82 (35–188)
52		3′-OMe	H	Me	0%	85 (45–188)
53		2′-OMe	H	Me	0%	155 (109–218)
54		4′-NH_2	H	Me	76%	24 (16–35)

Table III (Continued)

compd	Z	R′	R_a	R_2	PG synthetase inhibition in vitro: IC_{50}, μm, or inhibition at 30 μm	ACh writhing inhibition: ED_{50},[b] mg/kg po
55		3′-NH_2	H	Me	36%	16 (9–29)
56		4′-F	H	Me	73%	(60% at 238)
57		3′-F	H	Me	0%	(30% at 100)
58		4′-Me	H	Me	74%	29 (17–44)
59		3′-Me	H	Me	29%	(20% at 100)
60		2′-Me	H	Me	14%	88 (54–146)
61		4′-OEt	H	Me	35%	(53% at 300)
62		4′-OH	H	Me	36%	83 (47–158)
63		4′-H	H	Me	56%	28 (19–40)
64		4′-SMe	H	Me	87%	22 (12–35)
65		4′-SOMe	H	Me	0%	20 (12–35)
naproxen					6.7 (1.50–30)	10.9 (4.2–29)
ketoroloac					0.23 (0.17–0.32)	1.1 (0.43–3.7)

[a] See ref 12 for experimental procedures. [b] The vehicle was gum tragacanth, acidified water, or acidified dextrose. [c] 95% confidence limits. [d] NT: not tested.

Table IV. Ultraviolet Spectral Data



compd	R	absorption maximum (extinction coefficient)[a] (nm)
6a	H	223 (20800), 281 (7330)
73	CHO	213 (25500), 248 (15200), 267 (10500), 306 (15800)
63	COC_6H_5	215 (37000), 249 (13900), 276 (8200), 322 (9500)

[a] Spectra were measured in 95% EtOH.

the mixture was filtered to give a pink solid. The solid was suspended in 2 L of MeOH, 29 g of NaOH in 200 mL of H_2O was added, and the mixture was refluxed for 4 h to saponify N-acylated byproduct. The mixture was filtered, and the solids were washed with H_2O and then with Et_2O. After drying under vacuum, 113 g (85%) of **16** as a pink solid was obtained. An analytical sample was prepared by recrystallization from DMF/H_2O to give white crystals, mp 215–217 °C. Anal. ($C_{17}H_{15}NO_2$) C, H, N.

(4-Methoxyphenyl)[2-methyl-1-[2-(4-morpholinyl)ethyl]-1*H*-indol-3-yl]methanone (1a). A mixture of 20.65 g (78 mmol) of **16**, 25 g (130 mmol) of 4-(2-chloroethyl)morpholine hydrochloride, and 42 g (300 mmol) of milled potassium carbonate in 200 mL of DMF was heated on a steam bath for 24 h. The reaction mixture was concentrated under vacuum and the residue was taken up in H_2O. The solids that separated were filtered and washed with water to afford 28.7 g of a gray solid. Recrystallization from 2-PrOH gave 17.0 (58%) of white crystals. An analytical sample was prepared by recrystallization from EtOAc/hexane (1:1), mp 104–105 °C. Anal. ($C_{23}H_{26}N_2O_3$) C, H, N. The maleic acid salt (**1b**) crystallized from EtOH, mp 161–163 °C. Anal. ($C_{23}H_{26}N_2O_3 \cdot C_4H_4O_4$) C, H, N.

(4-Aminophenyl)[2-methyl-1-[2-(4-morpholinyl)ethyl]-1*H*-indol-3-yl]methanone (54). A mixture of 28.0 g (71 mmol) of **71** (Table VI), 0.30 g of PtO_2, 100 mL of glacial AcOH, and 100 mL of EtOAc was hydrogenated at 50 psi H_2 pressure on a Parr shaker at room temperature for 1.5 h. The mixture was then filtered through Celite and concentrated. The residue was dissolved in H_2O, and the solution was made basic with 10% aqueous NaOH and then extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and filtered through Celite, and the filtrate was concentrated to give a foam. Crystallization from EtOAc gave 19.05 g (74%) of a yellow solid, **54**, mp 154–156 °C. Anal. ($C_{22}H_{25}N_3O_2$) C, H, N.

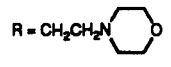
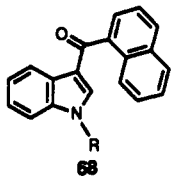
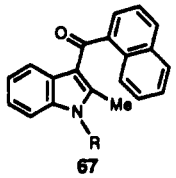
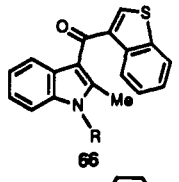
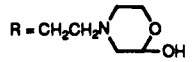
(3-Aminophenyl)[2-methyl-1-[2-(4-morpholinyl)ethyl]-1*H*-indol-3-yl]methanone (55). In a procedure analogous to the synthesis of **54**, **70** (Table VI) was hydrogenated over PtO_2 in AcOH and EtOAc in 83% yield, mp 167–169 °C (from EtOAc). Anal. ($C_{22}H_{26}N_3O_2$) C, H, N.

(4-Hydroxyphenyl)[2-methyl-1-[2-(4-morpholinyl)ethyl]-1*H*-indol-3-yl]methanone (62). The precursor **72** was debenzylated with H_2 over 5% Pd/C in EtOH. The hydrochloride salt crystallized from H_2O, mp 286–288 °C. Anal. ($C_{22}H_{24}N_2O_3 \cdot HCl$) C, H, N.

2-Methyl-1-[2-(4-morpholinyl)ethyl]-1*H*-indole (6a). To a stirred suspension of 229.5 g (1.22 mol) of *N*-(2-chloroethyl)-morpholine hydrochloride in 300 mL of DMSO was added rapidly 200 g (3.03 mol) of 85% KOH pellets. After the creamy suspension was stirred for 5 min, a solution of 133.7 g (1.0 mol) of 2-methylindole in 140 mL of DMSO was added dropwise without external cooling. An exotherm developed and after 20 min the temperature of the dark brown solution had reached 60 °C. The temperature was allowed to rise to 78 °C before cooling externally with cold H_2O. After 5 min of cooling, the temperature dropped to 75 °C, the bath was removed, and the reaction was stirred and gradually cooled to ambient temperature. After 3.5 h the reaction was diluted with 1 L of H_2O and 500 mL of toluene. The organic layer was separated and washed twice with 300 mL of H_2O. After drying the organic layer over $MgSO_4$ and filtration, the solution was evaporated under reduced pressure to give a dark oil. The oil was dissolved in 500 mL of heptane at 40 °C and cooled to ambient temperature to give 224 g (91%) of a tan crystalline product. An analytical sample was prepared by recrystallization from heptane, mp 65–67 °C. Anal. ($C_{15}H_{20}N_2O$) C, H, N.

4-[2-(1*H*-Indol-1-yl)-1-oxopropyl]morpholine (9). To 44 mL (0.5 mol) of morpholine in 140 mL (1 mol) of triethylamine

Table V. Antinociceptive AAIs Which Lack PG Synthetase Inhibitory Activity[a]

compd	MVD inhibition: IC_{50},[b] μm	ACh writhing inhibition:[c] ED_{50}, mg/kg iv	po
	0.006 ± 0.001	0.12 (0.08–0.18)[d]	23 (15–34)
 **68**			
 **67**	0.015 ± 0.001	0.19 (0.12–0.32)	97 (54–172)
 **66**	0.018 ± 0.004	60% at 30	106 (67–162)
	0.57 ± 0.13	9.7 (7–13)	50% at 1000
 **69**			

[a] See ref 12 and 23 for experimental procedures. [b] Mean ± SEM. [c] The vehicle was acidified water, acidified dextrose, or saline. [d] 95% confidence interval.

and 500 mL of CH_2Cl_2 was added 50 mL (0.5 mol) of 2-bromopropionyl chloride in 50 mL of CH_2Cl_2 over 1 h at 0 °C. The mixture was allowed to warm to ambient temperature and stirred for 2 h. The mixture was poured into 2 N HCl over ice, and the organic phase was washed with 5 portions of H_2O and once with brine, then dried over $MgSO_4$, and concentrated to afford 95 g (86%) of crude α-bromomorpholinopropanamide as a light brown oil. [Caution: this material is an irritant and lachrymator.]

To a mechanically stirred suspension of 10.8 g (0.27 mol) of NaH in 500 mL of DMF under N_2 at 0 °C was added over 45 min 28.7 g (0.246 mol) of indole in 200 mL of DMF. The mixture was allowed to warm to ambient temperature and stirred for 1 h. The mixture was cooled to 0 °C and 60 g (0.27 mol) of the above crude morpholinamide in 200 mL of DMF was added dropwise over 1 h. After the mixture was stirred for 3 h at ambient temperature, 300 mL of H_2O and 1.5 L of EtOAc was added. The organic phase was washed with 5 portions of H_2O and once with brine, dried over $MgSO_4$, and concentrated, yielding an oil. Trituration with EtOAc/Et_2O induced crystallization. Recrystallization from 2-PrOH yielded 35 g (55%) of a crystalline solid, mp 92–94 °C. Anal. ($C_{15}H_{18}N_2O_2$) C, H, N.

1-[1-Methyl-2-(4-morpholinyl)ethyl]-1*H*-indole (6b). To a mechanically stirred suspension of 3.12 g (78.44 mmol) of $LiAlH_4$ in 100 mL of Et_2O and 100 mL of THF under N_2 was added a solution of 20 g (7.75 mmol) of **9** in 300 mL of Et_2O over 2 h. The mixture was refluxed for 4 h and then cooled to ambient temperature and stirred for 16 h. Excess hydride was carefully destroyed by adding 3 mL of H_2O. This was followed by the addition of 3 mL of 10% NaOH and 9 mL of H_2O. The resulting suspension was stirred for 45 min. The mixture was filtered through a pad of anhydrous $MgSO_4$ and the filtrate concentrated to give an oil which crystallized as a white solid. Recrystallization from Et_2O/hexane (1:1) yielded 11.4 g (60%) of **6b**, mp 35–37 °C. Anal. ($C_{15}H_{20}N_2O$) C, H, N.

(−)-(*R*)-(2-Fluorophenyl)[1-[1-methyl-2-(4-morpholinyl)ethyl]-1*H*-indol-3-yl]methanone (30). To a stirred solution of 36 g (0.147 mol) of (+)-(*R*)-**6b** in 500 mL of CH_2Cl_2 was added 30 g (0.184 mol) of 2-fluorobenzoyl chloride. The mixture was stirred at 20 °C and 40 g (0.30 mol) of $AlCl_3$ was added in portions over 20 min via a gooch tube (a mild reflux occurred after several minutes). The reaction mixture was stirred for 15 min and then basified to pH 11 and diluted further with 200 mL of EtOAc. The organic layer was washed with 250 mL of H_2O and the solvent was evaporated under reduced pressure. The red residual syrup was crystallized from 200 mL of MeOH to afford an off-white solid. The mother liquor was purified by flash chromatography on 20 g of SiO_2 eluting with CH_2Cl_2/hexane (1:1). The combined crystalline free base was converted to the HCl salt and recrys-

Table VI. Compounds Prepared by Path a, Scheme I

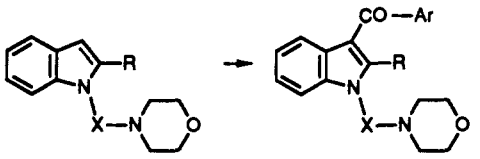
compd	% yield for step: 1	2	formula	recrystn solvent	mp, °C	analysis
61	73	68	$C_{24}H_{28}N_2O_3$	2-PrOH	93–97	C,H,N
53	75	89	$C_{23}H_{26}N_2O_3 \cdot MeSO_3H$	2-PrOH/Et_2O	199–214	C,H,N
52	63	84	$C_{23}H_{26}N_2O_3$	EtOAc	130–131	C,H,N
56	76	80	$C_{22}H_{23}FN_2O_2 \cdot MeSO_3H$	EtOH	209–211	C,H,N
57	64	77	$C_{22}H_{23}FN_2O_2$	2-PrOH	130–131	C,H,N
24	85		$C_{22}H_{23}FN_2O_2$	2-PrOH	112–114	C,H,N
58	60	75	$C_{23}H_{26}N_2O_2$	EtOAc	121–122	C,H,N
63	64	59	$C_{24}H_{24}N_2O_2$	EtOAc/hexane	111–112	C,H,N
50	80	55	$C_{22}H_{24}N_2O_3 \cdot MeSO_3H$	MeOH	110–112	C,H,N[a]
67	99	42	$C_{26}H_{26}N_2O_2$	2-PrOH	122–124	C,H,N
66[b]	36	64	$C_{24}H_{24}N_2O_2S \cdot MeSO_3H \cdot H_2O$	EtOH/Et_2O	201–208	C,H,N,S[c]
64	36	37	$C_{23}H_{26}N_2O_2S$	EtOAc/hexane	125–126	C,H,N
65[d]		69	$C_{23}H_{26}N_2O_3 \cdot {}^1/_4H_2O$	EtOAc/hexane	103–105	C,H,N[e]
			7: R_2 = Me, R = H, X = 4-morpholinyl			
Ar = 4′-$NO_2C_6H_4$:						
70[f]	42	72				
Ar = 3′-$NO_2C_6H_4$:						
71[f]	23	64				
Ar = 4′-$C_6H_5OC_6H_4$:						
72	39	69	$C_{29}H_{30}N_2O_3$	EtOH	140–141	C,H,N

[a] Anal. Calcd for $C_{22}H_{24}N_2O_3 \cdot MeSO_3H \cdot H_2O$: C, 57.73; H, 6.32; N, 5.85. Found: C, 57.46; H, 6.56; N, 5.77. [b] The requisite acid chloride was synthesized by established procedures (refs 25, 26). [c] Anal. Calcd for $C_{24}H_{24}N_2O_2S \cdot MeSO_3H \cdot H_2O$: C, 57.90; H, 5.83; N, 5.40; S, 12.36. Found: C, 58.11; H, 5.94; N, 5.34; S, 12.57. [d] Prepared by oxidation of corresponding step 1 acylated intermediate to **64** (MCPBA, $CHCl_3$, 69%), followed by N-alkylation. [e] Anal. Calcd for $C_{23}H_{26}N_2O_3S \cdot {}^1/_4H_2O$: C, 66.56; H, 6.44; N, 6.75. Found: C, 66.62, H, 6.50; N, 6.77. [f] This compound was used directly in a subsequent reduction step without purification.

Table VII. Tertiary Amines Prepared by Step d, Scheme I

compd	NR_1R_2	% yield	formula	recrystn solvent	mp, °C	analysis
37	1-piperidinyl	52	$C_{24}H_{28}N_2O_2 \cdot HCl$	$MeOH/Et_2O$	249–250	C,H,Cl,N
38	1-pyrrolidinyl	49	$C_{23}H_{26}N_2O_2 \cdot HCl$	$MeOH/Et_2O$	233–235	C,H,Cl,N
44	NMe_2	56	$C_{21}H_{24}N_2O_2 \cdot HCl$	$MeOH/Et_2O$	237–240	C,H,N
39	NEt_2	62	$C_{23}H_{28}N_2O_2 \cdot HCl$	$EtOAc/Et_2O$	209–211	C,H,N

Table VIII. Compounds Prepared by Path B, Scheme I



compd	R	X	Ar	% yield	formula	recrystn solvent	mp, °C	analysis
59	Me	$(CH_2)_2$	$3\text{-}MeC_6H_4$	42	$C_{23}H_{28}N_2O_2$	CH_2Cl_2/Et_2O	125–127	C,H,N
60	Me	$(CH_2)_2$	$2\text{-}MeC_6H_4$	72	$C_{23}H_{26}N_2O_2 \cdot HCl$	2-PrOH/Et_2O	245–247	C,H,N
51	Et	$(CH_2)_2$	$4\text{-}MeOC_6H_4$	88	$C_{24}H_{28}N_2O_3$	$EtOAc/Et_2O$	143.0–145.5	C,H,N
28[a]	H	$(CH_2)_2$	$2\text{-}FC_6H_4$	45	$C_{21}H_{21}FN_2O_2 \cdot HCl$	2-PrOH	210–212	C,H,N
68[b]	H	$(CH_2)_2$	1-naphthyl	62	$C_{25}H_{24}N_2O_2$	Et_2O	104–106	C,H,N
47[c]	Me	$(CH_2)_3$	$4\text{-}MeOC_6H_4$	38	$C_{24}H_{28}N_2O_2 \cdot MeSO_3H$	EtOH	153–155	C,H,N
(±)-**29**[b]	H	$CH(Me)CH_2$	$2\text{-}FC_6H_4$	73	$C_{22}H_{23}FN_2O_2$	2-PrOH	145–147	C,H,N
(+)-**31**[d]	H	$CH(Me)CH_2$	$2\text{-}FC_6H_4$	50	$C_{22}H_{23}FN_2O_2$	2-PrOH	139.5–140.5	C,H,F,N
(−)-**30**[e]	H	$CH(Me)CH_2$	$2\text{-}FC_6H_4$	59	$C_{22}H_{23}FN_2O_2$	2-PrOH	140–141	C,H,F,N
(±)-**25**[b,c]	Me	$CH(Me)CH_2$	$2\text{-}FC_6H_4$	73	$C_{23}H_{25}FN_2O_2$	2-PrOH	126–128	C,H,N
(+)-**26**[g]	Me	$CH(Me)CH_2$	$2\text{-}FC_6H_4$		$C_{23}H_{25}FN_2O_2 \cdot C_4H_4O_4$	EtOAc/hexane	140–143	C,H,F,N
(−)-**27**[h]	Me	$CH(Me)CH_2$	$2\text{-}FC_6H_4$	31	$C_{23}H_{25}FN_2O_2 \cdot C_4H_4O_4$	EtOAc/hexane	141.5–143.0	C,H,F,N
23	Me	$CH(Me)CH_2$	$4\text{-}MeOC_6H_2$	66	$C_{24}H_{28}N_2O_3$		amorphous	C,H,N

[a] $EtAlCl_2$ was used in place of $AlCl_3$ in the Friedel–Crafts reaction. [b] Dichloroethane was used in place of CH_2Cl_2 in the Friedel–Crafts reaction. [c] The precursor was prepared from 2-methylindole and morpholinylpropyl chloride analogous to the preparation of **6a**. [d] $[\alpha]^{25}_D$ = +5.4° (1%, $CHCl_3$). [e] $[\alpha]^{25}_D$ − 4.5° (1%, $CHCl_3$). [f] The precursor, **6c**, was prepared analogous to the preparation of 66. [g] $[\alpha]^{25}_D$ = −17.6° (1%, MeOH). [h] $[\alpha]^{25}_D$ = +17.5° (1% MeOH).

tallized from isopropyl acetate, which furnished 21.5 g (36%), mp 201–203 °C, $[\alpha]^{25}_D$ = −67.4° (*c* = 1.0, $CHCl_3$). Anal. ($C_{22}H_{24}ClFN_2O_2$) C, H. Enantiomeric purity was determined by HPLC (LKB enantiopac): ee = 97%. A second lot, characterized as the free base, is described in Table VIII.

2-Methyl-1-[2-(4-morpholinyl)ethyl]-1*H*-indole-3-carboxaldehyde (73). To 70 mL (66.08 g, 0.90 mol) of dry DMF at 0 °C under N_2 was added dropwise 15 mL (24.67 g, 0.161 mol) of $POCl_3$. After the mixture was stirred for 15 min, a solution of 24.6 g (0.1 mol) of **6a** in 50 mL of dry DMF was added. The cooling bath was removed and the reaction mixture was stirred at room temperature for 1 h. The mixture was then poured slowly over ice and neutralized with 150 mL of 35% aqueous KOH while the temperature was kept below 30 °C. The resulting mixture was heated to 70 °C and then cooled in an ice bath, yielding a colorless solid. The solid was filtered and washed with water. Recrystallization from EtOAc/hexane (1:1) gave 23.3 g (83%), mp 115–116 °C. Anal. ($C_{16}H_{20}N_2O_2$) C, H, N.

Resolution of 6b. A solution of 8 g (0.033 mol) of racemic **6b** in 280 mL of acetone was stirred with 12 g (0.032 mol) of (+)-dibenzoyl-D-tartaric acid monohydrate. The collected precipitate was recrystallized twice from acetone to afford 8.4 g (42%) of the dextrorotatory salt. An analytical sample was prepared by recrystallization from acetone to give a white solid, mp 145–146 °C, $[\alpha]_D$ = +65.1° (1%, MeOH). Anal. Calcd for $C_{15}H_{20}N_2O \cdot C_{18}H_{14}O_8 \cdot {}^1/_4H_2O$: C, 65.28; H, 5.72; N, 4.61. Found: C, 65.15; H, 5.55; N, 4.49.

To a stirred suspension of 79.2 g of the above dextrorotatory salt in 500 mL of H_2O at room temperature was added concentrated NH_4OH and the mixture was cooled and carefully extracted with Et_2O. The Et_2O layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated to afford 28.5 g (90%) of (−)-**6b**. A bulb-to-bulb distillation at 165–175 °C and 0.2 mm afforded 27.3 g of (−)-**6b**, $[\alpha]_D$ = −74.6° (0.5%, $CHCl_3$). Anal. ($C_{15}H_{20}N_2O$) C, H, N. The maleic acid salt was also prepared, mp 125–126 °C, $[\alpha]_D$ = −2.7° (1%, MeOH). Anal. ($C_{15}H_{20}N_2O \cdot C_4H_4O_4$) C, H, N.

In similar fashion, (+)-**6b** was obtained by resolution with (−)-dibenzoyl-L-tartaric acid monohydrate. An analytical sample was prepared by recrystallization from acetone to afford a white solid, mp 145–146 °C, $[\alpha]_D$ = −63.7° (1%, MeOH). Anal. Calcd for $C_{15}H_{20}N_2O \cdot C_{18}H_{14}O_8 \cdot {}^1/_4H_2O$: C, 65.28; H, 5.72; N, 4.61. Found: C, 65.36; H, 5.69; N, 4.52.

Data for the free base: bulb-to-bulb distillation at 170–175 °C at 0.1 mm, $[\alpha]_D$ = +78.0° (1%, $CHCl_3$). Anal. ($C_{15}H_{20}N_2O$) C, H, N. Data for the maleic acid salt, mp 125–126 °C, $[\alpha]_D$ = +2.5° (1%, MeOH).

Resolution of 6c. Similar to the resolution of **6b** above, (±)-**6c** was resolved with (+)-dibenzoyl-D-tartaric acid monohydrate from EtOAc, mp 113–121 °C, $[\alpha]_D$ = +57.5 (1%, MeOH). The free base had rotation $[\alpha]_D$ = −23.8° (1%, $CHCl_3$).

The enantiomer, (+)-**6c**, was obtained by resolution with (−)-dibenzoyl-L-tartaric acid monohydrate from EtOAc, mp 109–115 °C, $[\alpha]_D$ = −58.6° (1%, MeOH). The free base had rotation $[\alpha]_D$ = +20.1° (0.92%, $CHCl_3$).

(+)-(*R*)-4-[2-(1*H*-Indol-1-yl)-1-oxopropyl]morpholine ((+)-*R*-9). A solution of 7.6 g (40 mmol) of (+)-(*R*)-α-methyl-1*H*-indole-1-acetic acid[5] in 150 mL of THF was cooled to −15 °C under N_2 and 6.5 mL (45 mmol) of Et_3N was added. Pivaloyl chloride (5.5 g, 45 mmol) in 10 mL of THF was then added dropwise over 35 min and the reaction mixture stirred for 1 h in the cold. A solution of 4.0 g (45 mmol) of morpholine in 5 mL of THF was then added over 20 min and the mixture was stirred for another 1.5 h. The reaction was then concentrated under reduced pressure. The residue was diluted with Et_2O and washed sequentially with saturated aqueous $NaHCO_3$ and H_2O. Removal of the solvent gave a quantitative yield of (+)-*R*-**9**, which was recrystallized from $MeOH/H_2O$ (1:1) to afford 7.85 g (79%) of a white solid, mp 106–107 °C, $[\alpha]^{25}_D$ = +75.2° (1.0%, DMF). This material was determined to be 99% ee by GC analysis. Anal. ($C_{15}H_{18}N_2O_2$) C, H, N.

(+)-(*R*)-1-[1-Methyl-2-(4-morpholinyl)ethyl]-1*H*-indole ((+)-(*R*)-6b). A toluene solution of 2.6 g (100 mmol) of (+)-(*R*)-**9** was reduced with 6.0 g (190 mmol) of Vitride (70% in toluene). The product was recrystallized from Et_2O/hexane (1:1) to give 1.8 g (75%) of (+)-(*R*)-**6b**, mp 41–42 °C, $[\alpha]^{25}_D$ = +67.4° (1%, $CHCl_3$); determined to be 99% ee by HPLC analysis. Anal. ($C_{15}H_{20}N_2O$) C, H, N.

Conversion of (+)-(*R*)-6b to (−)-(*R*)-6c. To a solution of 730 mg (3.0 mmol) of (+)-(*R*)-**6b** in 15 mL of Et_2O at 5 °C was added 2.2 mL of 1.6 N *n*-BuLi in hexane under N_2. After stirring

for 1.5 h at room temperature, the mixture was again cooled to 5 °C and 0.22 mL (3.0 mmol) of MeI was added dropwise. The mixture was stirred for 2 h at room temperature and was then quenched by pouring into ice/water. The organic layer was washed with H_2O and concentrated to give 780 mg of a tan oil, which was contaminated with unreacted (+)-(*R*)-**6b**. Pure (−)-(*R*)-**6c** was obtained by flash chromatography on 100 g of silica gel. Recrystallization from hexane furnished 104 mg (15%) of a white solid, mp 65–66 °C, $[\alpha]^{25}_D = -25.6°$ (1.0%, $CHCl_3$). This material was determined to be >99% ee by HPLC analysis.

3-(4-Methoxybenzoyl)-2-methyl-1*H*-indole-1-acetic Acid (32). To a stirred solution of 25.0 g (0.094 mol) of **16** in 250 mL of DMF under N_2 was added 5.3 g (0.113 mol) of 50% NaH. After stirring for 30 min, the mixture was cooled and 12.5 mL (0.113 mol) of ethyl bromoacetate was added. The resulting red solution was stirred for 2.5 h and then diluted with 1.5 L of EtOAc. The organic layer was washed with 3 portions of 250 mL of H_2O, followed by saturated brine, and then dried over Na_2SO_4 and evaporated to dryness to give 41 g of a red oil. The oil was dissolved in 400 mL of EtOH, 100 mL of 10% NaOH was added, and the mixture was refluxed with stirring for 4 h. The reaction mixture was then cooled and diluted with H_2O. Acidification of the solution to pH 1.0 using concentrated HCl resulted in a solid which was recrystallized from EtOH to give 21.0 g (69%), mp 208–210 °C. Anal. ($C_{19}H_{17}NO_4$) C, H, N.

2-Methyl-3-(1-naphthoyl)-1*H*-indole-1-acetic Acid (74). This compound was prepared in a manner analogous to that used for the preparation of **32**. It was characterized as the sodium salt, mp >300 °C. Anal. ($C_{22}H_{16}NO_3Na$) C, H, N.

3-(2-Fluorobenzoyl)-α,2-dimethyl-1*H*-indole-1-acetic Acid (33). To a suspension of 2.4 g (0.06 mol) of 60% NaH in 100 mL of dry DMF under N_2 was added dropwise 12.5 g (0.05 mol) of (2-fluorophenyl)(2-methyl-1*H*-indol-3-yl)methanone (Table VI) in 100 mL of DMF over a 40-min period. The mixture was stirred for 1 h and then 7.8 mL (0.06 mol) of ethyl 2-bromopropionate in 100 mL of DMF was added rapidly. The mixture was heated on a steam bath for 3 h. The mixture was quenched with 100 mL of saturated NH_4Cl solution and extracted with EtOAc. The organics were washed sequentially with H_2O and saturated brine solution, dried over $MgSO_4$, filtered, and concentrated, yielding an oil. To this oil was added 300 mL of MeOH and 200 mL of 5 N NaOH and the resulting mixture was refluxed overnight. The cooled mixture was then concentrated, acidified with 6 N HCl, and extracted with EtOAc. The combined extracts were dried over $MgSO_4$, filtered, and concentrated, yielding a purple oil. The product was crystallized and then recrystallized from EtOAc, affording 10.2 g (63% for two steps) of **33**, mp 265–267 °C. Anal. ($C_{19}H_{16}FNO_3$) C, H, N.

[1-(4-Bromobutyl)-2-methyl-1*H*-indol-3-yl](4-methoxyphenyl)methanone (75). To a mechanically stirred solution of 60 g (0.23 mol) of **16** and 244 g (1.13 mol) of 1,4-dibromobutane in 200 mL of DMF at 0 °C under N_2 was added in portions 13.6 g (0.34 mol) of 60% NaH. The mixture was stirred overnight at ambient temperature. The reaction mixture was then poured into H_2O and extracted with EtOAc. The organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting bromide was used as is in the next transformation, without further purification. Purification was accomplished by preparative HPLC, eluting with hexane/EtOAc (3:1). An analytical sample was prepared by recrystallization from EtOAc/hexane, mp 83–86 °C. Anal. ($C_{21}H_{22}BrNO_2$) C, H, Br, N.

(4-Methoxyphenyl)[2-methyl-1-[4-(4-morpholinyl)butyl]-1*H*-indol-3-yl]methanone (48). A solution of 22.5 g (0.056 mol) of **75** and 12.2 g (0.141 mol) of morpholine in 300 mL of DMF was stirred overnight. The mixture was poured into H_2O and extracted with EtOAc. The organics were extracted with 2 N aqueous HCl. The aqueous extracts were made basic by the addition of 35% aqueous NaOH and extracted with EtOAc. The organics were washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. The product was purified by preparative HPLC, eluting with EtOAc, affording 10.6 g (47%) of **48**. An analytical sample was characterized as the hydrochloride salt, by recrystallization from MeCN, mp 208–211 °C. Anal. ($C_{25}H_{30}N_2O_3 \cdot HCl$) C, H, Cl, N.

(4-Methoxyphenyl)[2-methyl-1-[5-(4-morpholinyl)pentyl]-1*H*-indol-3-yl]methanone (49). In a procedure analogous to the preparation of **48**, the intermediate **6a** was treated first with 1-bromo-5-chloropentane and NaH in DMF and then with morpholine to provide **49** in 24% yield. An analytical sample was prepared as the hydrochloride salt, recrystallized from MeOH/Et_2O (1:1), mp 187–190 °C. Anal. ($C_{26}H_{32}N_2O_3 \cdot HCl$) C, H, Cl, N.

[1-(2-Hydroxyethyl)-2-methyl-1*H*-indol-3-yl](4-methoxyphenyl)methanone (17). To a suspension of 100 g (0.377 mol) of **16** in 700 mL of dry THF under N_2 at 0 °C was added 183.5 mL (0.385 mol) of 2.1 M *n*-BuLi dropwise over 1 h. The resulting homogeneous mixture was stirred at 0 °C for 1.5 h and then allowed to warm to ambient temperature for 30 min. The reaction was again cooled to 0 °C and 275.3 mL (0.58 mol) of a 3.67 M solution of ethylene oxide in THF was added dropwise over a 30-min period. The reaction was stirred for 1 h at 0 °C and then allowed to warm to ambient temperature and stirred for 72 h. The reaction was quenched with 200 mL of saturated NH_4Cl solution. EtOAc was added and the organic phase was washed with five portions of H_2O, once with saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford an orange oil. The oil was crystallized from CH_2Cl_2 and then recrystallized from EtOAc, yielding 90 g (75%) of **17**, mp 95–100 °C dec. Anal. Calcd for $C_{19}H_{19}NO_3 \cdot {}^1/_3H_2O$: C, 72.36; H, 6.29; N, 4.44. Found: C, 72.20; H, 6.37; N, 4.34.

[1-[2-(Acetyloxy)ethyl]-2-methyl-1*H*-indol-3-yl](4-methoxyphenyl)methanone (18). To 21 g (0.068 mol) of **17** in 140 mL of toluene was added 3.01 g (0.03 mol) of ptassium acetate and 6.72 mL (0.07 mol) of Ac_2O. The mixture was refluxed for 24 h and then poured into ice/H_2O. The organic layer was washed with four portions of H_2O, once with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated to a solid. This was recrystallized from EtOAc, affording 20 g (84%) of **18** as a tan solid, mp 98–100 °C. Anal. ($C_{21}H_{21}NO_4$) C, H, N.

4-[2-(Acetyloxy)ethyl]-9-methoxy-5-methylnaphth[3,2,1-*cd*]indol-6(4*H*)-one (19). To a solution of 22 g (0.063 mol) of **18** in 1 L of AcOH was added 7.04 g (0.031 mol) of palladium acetate. The mixture was refluxed for 24 h under N_2. The mixture was concentrated and then diluted with EtOAc and filtered through a pad of Celite. The Pd cake was thoroughly washed with EtOAc. The organic filtrate was washed with four portions of H_2O, once with saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated, yielding 22 g of a brown oil. This was purified by preparative HPLC eluting with EtOAc/hexane (3:1) to afford 16.3 g (74%) of **18** and 1.5 g (14%) of **19**, mp 181 °C. Anal. ($C_{21}H_{19}NO_4$) C, H, N.

4-(2-Hydroxyethyl)-9-methoxy-5-methylnaphth[3,2,1-*cd*]indol-6(4*H*)-one (20). To a suspension of 1.5 g (4.3 mmol) of **19** in 50 mL of CH_2Cl_2 and 150 mL of CH_3OH at 0 °C was added 25 mL of a saturated K_2CO_3/MeOH solution. The mixture became homogeneous. After 3–4 min at 0 °C, TLC analysis (100% EtOAc) indicated that the reaction was complete. The mixture was concentrated to a third of its original volume and then poured into ice/H_2O. The resulting light tan solid was collected and washed with H_2O and then with cold Et_2O to afford 1.2 g (91%) of **20**, mp 211–212 °C. This product was used as is in the next step, without further purification.

4-(2-Bromoethyl)-9-methoxy-5-methylnaphth[3,2,1-*cd*]indol-6(4*H*)-one (21). To 1.1 g (3.6 mmol) of **18** in 15 mL of MeCN was added 0.59 g (3.6 mmol) of *N,N'*-carbonyldiimidazole. The mixture was warmed briefly and then stirred at ambient temperature for 30 min after which 4.8 mL (54.3 mmol) of allyl bromide was added. The suspension was stirred for 30 min and then refluxed for 3 h. After standing overnight under N_2, the mixture was concentrated. To the concentrate was added CH_2Cl_2 and the organic layer was washed two times with 2 N H_2SO_4, once with dilute aqueous $NaHCO_3$, and once with saturated NaCl. The organics were dried over $MgSO_4$, filtered, and concentrated to afford a light green solid. The solid was recrystallized from CH_2Cl_2, affording 1.2 g (90%) of **21**.

9-Methoxy-5-methyl-4-[2-(4-morpholinyl)ethyl]naphth[3,2,1-*cd*]indol-6(4*H*)-one (22). To 1 g (2.7 mmol) of **21** in 50 mL of DMF was added 0.48 mL (5.4 mmol) of morpholine. The mixture was heated at 140 °C under N_2 for 24 h, after which TLC analysis (EtOAc) indicated that the reaction was complete. The mixture was diluted with CH_2Cl_2 and washed with five portions of H_2O. The organic phase was then acidified with 2 N H_2SO_4

Table IX. Analogues of 40 Prepared by a Similar Displacement Sequence

compd	NR_1R_2	% yield	formula	recrystn solvent	mp, °C	analysis
43	4-methylpiperazinyl	62	$C_{24}H_{29}N_3O_2$	CH_2Cl_2/EtOAc	110–112	C,H,N
41	3-hydroxypiperidinyl	62	$C_{24}H_{28}N_2O_3 \cdot HCl \cdot {}^1/_2H_2O$	EtOAc/Et_2O	160	C,H,N[f]
42	piperazinyl[a,b]	64	$C_{23}H_{27}N_3O_2 \cdot 2MeSO_3H$	EtOH	240	C,H,N
45	NH_2[c,d]	75	$C_{19}H_{20}N_2O_2 \cdot C_4H_4O_4$	EtOH/Et_2O	165–166	C,H,N
46	NHEt[e]	50	$C_{21}H_{24}N_2O_2 \cdot C_4H_4O_4$	EtOH	180–181	C,H,N

[a] Piperazine, DMF, 100 °C, 16 h. [b] NaOH, EtOH, reflux, 4 h. [c] NaN_3, H_2O, acetone, reflux, 72 h. [d] 10% Pd/C, H_2, EtOH, THF. [e] $EtNH_2$, H_2O·DMF, 100 °C, 16 h. [f] Anal. Calcd for $C_{24}H_{28}N_2O_3 \cdot HCl \cdot {}^1/_2H_2O$: C, 65.82; H, 6.90; N, 6.40. Found: C, 65.82; H, 7.15, N, 6.27.

and extracted three times with H_2O. The combined aqueous extracts were made alkaline with NH_4OH and extracted three times with CH_2Cl_2. The combined organics were washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated to an oil. Treatment with EtOAc/Et_2O (1:1) yielded a crystalline solid which was then dissolved in EtOAc and passed through a short column of Florisil. Recrystallization from EtOAc/Et_2O (1:1) yielded 600 mg (59%) of **22**, mp 178.0–179.5 °C. Anal. ($C_{23}H_{24}N_2O_3$) C, H, N.

[2-Methyl-1-[2-[[(4-methylphenyl)sulfonyl]oxy]ethyl]-1*H*-indol-3-yl](4-methoxyphenyl)methanone (7a). Analogous to the synthesis of 17, 5 g (18.9 mmol) of 16 in 40 mL of THF was reacted with 9.17 mL (19.2 mmol) of 2.1 M *n*-BuLi in hexane and 7.8 mL (28.8 mmol) of 3.67 M ethylene oxide in THF. The mixture was stirred for 48 h and then cooled to 0 °C, and 4.5 g (23.6 mmol) of tosyl chloride in 35 mL of THF was added in one portion. The mixture was allowed to warm to ambient temperature and stirred for 24 h. The mixture was quenched with saturated NH_4Cl solution. Volatiles were removed under reduced pressure, and the resulting mixture was extracted with EtOAc. The organics were washed with H_2O and saturated brine, dried over $MgSO_4$, filtered, and concentrated to an oil. The oil was chromatographed on 200 g of silica gel, eluting with a gradient of hexane, progressing to 20% EtOAc/hexane. Treatment of the resulting oil with EtOAc afforded 5.0 g (57%) of **7a** as a foam, mp 62–65 °C. Anal. ($C_{26}H_{25}NO_5S$) C, H, N.

[1-[2-(4-Hydroxy-1-piperidinyl)ethyl]-2-methyl-1*H*-indol-3-yl](4-methoxyphenyl)methanone (40). To a solution of 1.7 g (3.73 mmol) of **7a** in 10 mL of dry MeCN was added an excess (14.9 mmol) of 4-hydroxypiperidine. The mixture was refluxed under N_2 for 24 h after which TLC analysis (10% MeOH/$CHCl_3$) showed the reaction to be complete. The mixture was concentrated, EtOAc was added, and the solution was extracted three times with 2 N HCl. The combined aqueous extracts were made alkaline with 10% NaOH and extracted three times with EtOAc. The combined organics were washed with saturated brine solution, dried over $MgSO_4$, filtered, and concentrated to an oil. The oil was dissolved in EtOAc and treated with ethereal HCl. The resulting solid was filtered and washed with Et_2O to afford 1.5 g (92%) of **40**, mp 226–229 °C. Anal. Calcd for $C_{24}H_{28}N_2O_3 \cdot HCl \cdot {}^1/_2H_2O$: C, 65.82; H, 6.90; N, 6.40. Found: C, 65.57; H, 6.92; N, 6.46.

[1-[2-(3-Hydroxy-1-piperidinyl)ethyl]-2-methyl-1*H*-indol-3-yl](1-naphthalenyl)methanone (69). In a procedure analogous to the preparation of **40**, a THF solution of (2-methyl-1*H*-indol-3-yl)(1-naphthalenyl)methanone (Table VI) was treated sequentially with *n*-BuLi and ethylene oxide in THF and then with tosyl chloride. The tosylate was reacted with 3-hydroxypiperidine to afford **69** (20% overall yield). An analytical sample was prepared by recrystallization from 2-PrOH, mp 175–180 °C. Anal. Calcd for $C_{27}H_{28}N_2O_2 \cdot HCl \cdot H_2O \cdot {}^1/_6C_3H_8O$: C, 69.24; H, 6.83; N, 5.87. Found: C, 69.57; H, 6.94; N, 5.95.

5,10-Dihydro-5-[2-(4-morpholinyl)ethyl]indeno[1,2-*b*]indole (14). To a suspension of 5.0 g (0.104 mol) of 50% NaH in 100 mL of dry DMF under N_2 at 0 °C was added dropwise a solution of 19.0 g (0.1 mol) of indenoindole **13**.[7] The mixture was stirred at 0 °C for 1 h and then at room temperature for another hour. A solution of the free base of *N*-(2-chloroethyl)morpholine (obtained from the HCl salt by extraction between saturated $NaHCO_3$/Et_2O) in 100 mL of dry DMF was added dropwise and the mixture stirred at room temperature for 18 h. The reaction mixture was treated with glacial AcOH and the resulting solution was evaporated to dryness, diluted with H_2O, and extracted with CH_2Cl_2. The organics were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 33.7 g (95%) of a brown oil which crystallized upon standing. An analytical sample was prepared as the maleic acid salt by recrystallization from MeOH, mp 201–203 °C. Anal. ($C_{21}H_{22}N_2O \cdot C_4H_4O_4$) C, H, N.

5-[2-(4-Morpholinyl)ethyl]indeno[1,2-*b*]indol-10(5*H*)-one (15). To a solution of 12.6 g (0.04 mol) of 14 in 100 mL of dry THF under N_2 at room temperature was added 4.6 g (0.048 mol) of 3,5-dimethylpyrazole followed by 2.3 g (0.048 mol) of 50% NaH.[8] The reaction mixture was stirred under N_2 for 1 h, and then the reaction flask was opened to air while stirring was continued for 24 h. The solvent was removed under reduced pressure and the residue was partitioned between H_2O and CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness to afford 12.3 g of a dark semisolid. This product was dissolved in hot CH_3OH and 1 M CH_3SO_3H solution in CH_3OH was added until pH ~3. After cooling to ambient temperature a red-yellow solid precipitated, which was recrystallized from MeOH/Et_2O (1:1) to give 10.8 g (68%) of **15**, mp 278–280 °C. Anal. ($C_{21}H_{20}N_2O_2 \cdot CH_3SO_3H$) C, H, N.

5,6,7,12-Tetrahydro-5-[2-(4-morpholinyl)ethyl]benzo[4,5]cyclohept[1,2-*b*]indole (11). To a suspension of 25 g (0.064 mol) of 60% NaH under N_2 at 0 °C was added dropwise a solution of 10.0 g (0.043 mol) of 1,4,7,8-tetrahydro-1-azadibenz[*b*,*f*]azulene (**10**)[6] in 160 mL of dry DMF. The reaction mixture was stirred at 0 °C for 1 h and then for another hour at room temperature. A solution of the free base of 4-(2-chloroethyl)morpholine (prepared from 16.0 g (0.086 mol) of the hydrochloride salt and $NaHCO_3$ solution) in 50 mL of dry DMF was added slowly and the mixture was stirred at room temperature for 20 h. The mixture was then heated on a steam bath for 1 h and cooled to room temperature. After neutralization with glacial AcOH, the volatiles were removed under reduced pressure. The residue was partitioned between CH_2Cl_2 and H_2O. The organic layer was dried over $MgSO_4$ and evaporated to dryness to give 12.6 g (84%) of a tan solid. An analytical sample was characterized as the hydrochloride salt by recrystallization from MeOH/Et_2O (1:1), mp 244 °C dec. Anal. ($C_{23}H_{26}N_2O \cdot HCl$) C, H, N.

6,7-Dihydro-5-[2-(4-morpholinyl)ethyl]benzo[4,5]cyclohept[1,2-*b*]indol-12(5*H*)-one (12). To a solution of 5.11 g (0.0156 mol) of 11 in 66.3 mL of 90% aqueous THF at 0 °C under N_2 was added 7.1 g (0.0311 mol) of DDQ. The reaction mixture was stirred for 1 h and then diluted with EtOAc. The aqueous layer was extracted three times with EtOAc, and the combined extracts were dried over $MgSO_4$ and filtered. Removal of solvent gave a dark product which was passed through a neutral alumina column, eluting with EtOAc to afford 2.0 g (36%) of a yellow solid. An analytical sample was prepared by recrystallization from EtOAc, mp 131–132 °C. Anal. ($C_{23}H_{24}N_2O_2$) C, H, N.

Metabolism Studies. Concentrations of **1a**, **30**, and **67** and their metabolites were determined in plasma of male Swiss-Webster mice (18–24 g) by HPLC using validated methods via calibration from standard solutions. The vehicle for po administration of **30** was 1% gum tragacanth (dose volume of 10 mL/kg), for **67** the vehicle was dilute lactic acid (dose volume of 10 mL/kg), and for **1a** it was H_2O with a minimum volume of lactic acid.

In each case following CO_2 anesthesia, blood was collected via cardiac puncture into tubes containing potassium oxalate anticoagulant such that three samples (each consisting of pooled blood from three mice) per dose per time were obtained. After centrifugation, plasma was collected and stored frozen prior to analysis. Sample preparations for **1a** and **30** were carried out, mixing 200 μL of plasma and 400 μL of 0.05 N HCl and extracting the resultant mixture with Et_2O (2 × 5 mL). The Et_2O layers were pooled and evaporated to dryness under N_2, and the residues were reconstituted in 1 mL of mobile phase. Sample preparation

for 74 was carried out by mixing 0.2 mL of plasma with 0.8 mL of 0.026 M NH_4OAc in 82% MeOH and for 67 by mixing 0.2 mL of plasma with 0.8 mL of MeOH. The samples were allowed to stand for 10 min and centrifuged, and aliquots of the clarified supernatants were injected into the HPLC chromatographic system.

At 5 min following iv administration of **1a** at 1, 3, and 10 mg/kg, mean plasma concentrations of **1a** were 0.28 ± 0.01, 0.79 ± 0.16, and 4.6 ± 3.3 μg/mL, respectively. Those of the corresponding carboxylic acid metabolite, **32**, were 0.15 ± 0.04, 0.56 ± 0.06, and 1.23 ± 0.31 μg/mL, respectively (n = 3, each consisting of pooled blood from three mice). Following oral administration of **67** at 300 mg/kg, mean plasma concentrations of parent drug were below the minimum quantifiable level (MQL) of 0.068 μg/mL at time points ranging from 0.25 to 8.0 h, whereas a mean maximum concentration (C_{max}) of 5.04 ± 0.74 μg/mL of the acid metabolite **74** was achieved at 1 h. The concentration of this metabolite at 8 h, the last time point examined, was still 2.7 ± 0.4 μg/mL (n = 3, each consisting of pooled blood from three mice). Mean C_{max} values of the parent drug achieved following oral administration of **30** at 30, 100, 300, and 1000 mg/kg were below the MQL, 0.34 ± 0.10, 1.44 ± 0.32, and 1.52 ± 0.27 μg/mL of the parent drug, respectively, and of the acid metabolite were 4.1 ± 0.13, 10.3 ± 0.78, 18.6 ± 2.3, and 17.6 ± 1.3 μg/mL of the acid metabolite **34**, respectively. (These experiments were performed utilizing HPLC conditions which did not distinguish between the enantiomers of **34**.)

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Supplementary Material Available: X-ray crystallographic data for compounds **1a** and **1b** (12 pages). Ordering information is given on any current masthead page.

Synthesis and Structure–Activity Relationship of New Cephalosporins with Amino Heterocycles at C-7. Dependence of the Antibacterial Spectrum and β-Lactamase Stability on the pK_a of the C-7 Heterocycle

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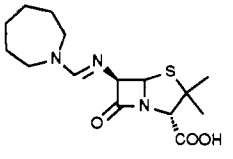
Cephalosporins with new aminobenzimidazole and aminoimidazoline heterocycles at C-7 have been synthesized starting with versatile C-7 isocyanide dihalide synthons. The aminobenzimidazoles have a broad spectrum of antibacterial activity, including Gram-positive and Gram-negative organisms, but possess limited β-lactamase stability. In contrast, the aminoimidazolines have a narrow spectrum of antibacterial activity, limited to Gram-negative strains only, but possess outstanding β-lactamase stability. Structure–activity relationships are discussed in terms of their dependence on the pK_a of the C-7 amino heterocycle, basic C-7 residues giving cephalosporins with exceptional β-lactamase stability.

Modification of the C-6 and C-7 acylamino residue in penicillins and cephalosporins is still, after decades of work, a very active and fruitful area of investigation.[1] Introduction of nonamidic C-6, C-7 substituents on penicillins and cephalosporins has also been performed over the years.[2] Variable levels of biological activity have been found, but in general, this approach has only been moderately successful. Indeed, all the therapeutically useful cephalosporins have acylamino C-7 chains. This is also true for the penicillins, with only one exception, mecillinam, a C-6 amidino penicillin.[3]



MECILLINAM

An intriguing feature of mecillinam is its highly selective affinity for penicillin binding protein 2 (PBP2), in contrast to amidic penicillins or cephalosporins which display a much broader pattern of affinity for the various PBPs.[4]

We were attracted by the interesting possibility that β-lactam antibacterials with an original mode of action could be devised by introduction of nonamidic C-6 or C-7 substituents in penicillins or cephalosporins. Cephalosporins with C-7 amino heterocycles of various basicities were selected as our initial targets.

Chemistry

Isocyanide Dihalide Chemistry. Isocyanide dihalides are well-known, powerful electrophiles, easily prone to a variety of nucleophilic displacement reactions leading to monocyclic or polycyclic heterocycles.[5]

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