peptidyltransferase target remains to be determined.

UV spectra of **1b** in aqueous solution (pH 7) and ethanol are almost superimposable, which indicates a lack of effective interaction (stacking) between both aromatic portions.[21] Similar conclusions can also be drawn from CD spectra showing a greater molecular ellipticity in ethanol than in water. It is, therefore, likely that the conformation of **1b** is "extended" as found, e.g., in puromycin.[22] Further biological testing of **1b**, along with the synthesis of additional hybrid antibiotics, is the subject of our present investigation.

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(21) In systems that are extensively stacked in aqueous solutions, as evidenced by hypochromism, a considerable destacking, and, hence, an increase of extinction coefficient, occurs in ethanol: (a) Browne, D. T.; Eisinger, J.; Leonard, N. J. *J. Am. Chem. Soc.* **1968**, *90*, 7302–7323.

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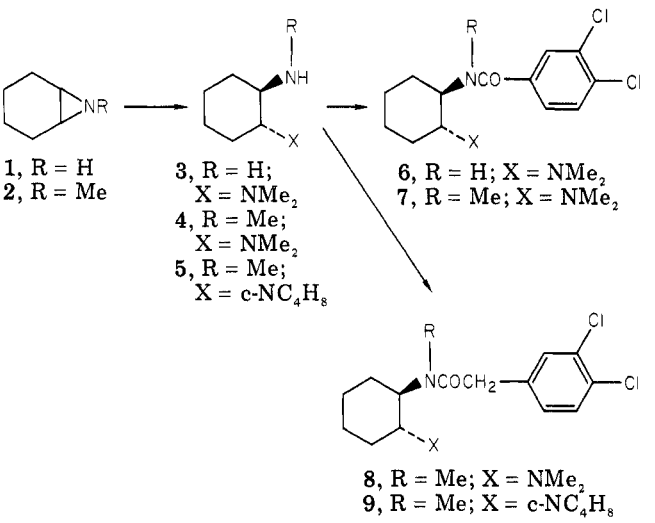
Benzeneacetamide Amines: Structurally Novel Non-mμ Opioids

Sir:

Studies with endorphins[1,2] and benzomorphans[3] have led to the hypothesis of multiple opioid receptors. The understanding of the functional significance of particularly the non-mμ (non-morphine receptive) receptors has been hampered by the scarcity of selective agonists and antagonists. We report here the prototype of a new series of opioid analgesics that does not have other morphine-like or narcotic antagonist effects. We also highlight the close structural similarity of this compound to compounds with potent mμ properties.

We have recently described our work with cycloalkane-1,2-diamines which led to potent antidepressant-like agents.[4] Inclusion of the benzamide and benzeneacetamide structural moieties in the *trans*-cyclohexane-1,2-diamine class of compounds led us to the discovery of a novel class of analgesics.

Scheme I



1, R = H
2, R = Me

3, R = H; X = NMe_2
4, R = Me; X = NMe_2
5, R = Me; X = c-NC_4H_8

6, R = H; X = NMe_2
7, R = Me; X = NMe_2

8, R = Me; X = NMe_2
9, R = Me; X = c-NC_4H_8

The structures and results of biological testing[5] in Table I briefly summarize the evolution of the structure–activity relationships (SAR) of this series. In mice, the benzamide **6** was discovered to have morphine-like analgesic and behavioral properties but lower potency than morphine. Methylation of the amide nitrogen afforded compound **7** and resulted in a considerable increase in analgesic potency but retention of morphine-like behavioral properties. The benzeneacetamide analogues (**8** and **9**), however, displayed no such behavioral effects but retained analgesic properties. In this regard, the pyrrolidine (**9**) is somewhat more potent subcutaneously than the dimethylamino comopund **8** and much more potent orally (tail-flick ED_{50} = 16 and >100 mg/kg, respectively). The apparent analgesic properties of these novel compounds are not the result of motor incapacitation, since the analgesic ED_{50}'s are well divorced from the gross sedative (inclined screen) ED_{50}. None of these compounds displayed morphine antagonist activity.

Further studies with **9** indicate that despite lacking mμ behavioral properties (Straub tail, arched back and increased locomotor activity), it is an opioid analgesic as defined by antagonism by the opioid antagonist naloxone. For example, 0.8 mg/kg of naloxone hydrochloride blocks the tail-flick analgesic effect of 25 mg/kg of **9**. Extensive biological evaluation[6] has confirmed the non-mμ opioid nature of **9** and suggested that it is a highly selective agonist for the so-called κ opioid receptor. As a structurally novel nonpeptide agonist, this compound may be a useful tool for delineating the functions of κ receptors. The close structural similarity of **8** and **9** to a potent mμ agonist (**7**) also offers the opportunity to understand the different steric requirements of these subpopulations of opioid receptors. Lastly, the benzeneacetamide amines may prove to be useful analgesics lacking many of the undesirable properties of morphine and the benzomorphans. This is

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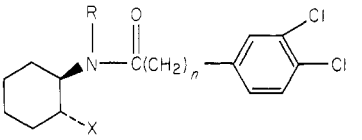
Table I. Biological Evaluation[a] of Benzamide and Benzeneacetamide Amines



compd	X	R	n	ED_{50},[b] mg/kg sc: tail flick	tail pinch	inclined screen	HCl writhing	morphine antagonism	narcotic stimulation[c]
6	$N(CH_3)_2$	H	0	11	11	>100	9	>100	+
7	$N(CH_3)_2$	CH_3	0	0.2	0.2	9	0.2	>100	+
8[d]	$N(CH_3)_2$	CH_3	1	2.8	7.0	>100	3.1	>100	–
9[e]	c-NC_4H_8	CH_3	1	2.5	2.5	71	2.5	>100	–
morphine sulfate				1.5	1.6	>50	0.6	>50	+

[a] Antinociceptive (tail flick, tail pinch, and HCl writhing), sedative (inclined screen), narcotic antagonist (morphine antagonism), and gross behavioral (narcotic stimulation) actions. [b] The upper and lower 95% confidence intervals were not more than 2 and less than 0.5 times the ED_{50}, respectively. [c] At least 3/6 mice observed at any dose (from subanalgesic to 100 mg/kg) to display Straub tail, arched back, and increased locomotor activity. [d] Tested as the *p*-toluenesulfonic acid salt. [e] Tested as the hydrochloride hemihydrate.

supported by observations that **9** is not self-administered nor does it induce opiate physical dependence in rodents.[7]

Syntheses. The synthetic methods are shown in Scheme I. Reaction of the aziridine **1**[8] with dimethylamine gave the trans diamine **3**.[9] Condensation of **3** with 3,4-dichlorobenzoyl chloride in ether in the presence of triethylamine gave 3,4-dichlorobenzamide **6**, mp 145–146 °C.[10]

Reaction of diamine **3** with ethyl formate gave *trans-N*-[2-(dimethylamino)cyclohexyl]formamide, bp 104 °C (0.1 mm).[10] Reduction with lithium aluminum hydride in ether led to *N,N,N'*-trimethyl-1,2-cyclohexanediamine **4**, bp 86–87 °C (14 mm).[10] Reaction of **4** with 3,4-dichlorobenzoyl chloride gave 3,4-dichlorobenzamide **7**, mp 97–98.5 °C.[10]

Reaction of 3,4-dichlorophenylacetic acid with 1,1'-carbonyldiimidazole in tetrahydrofuran, followed by diamine **4**, afforded the 3,4-dichlorophenylacetamide **8**, isolated as the *p*-toluenesulfonic acid salt, mp 203-204 °C.[10]

Reaction of the *N*-methylaziridine **2**[11] with pyrrolidine gave the diamine **5**, bp 118–119 °C (13 mm),[10] which was converted to the 3,4-dichlorophenylacetamide derivative **9**, isolated as the hydrochloride hemihydrate, mp 205–206 °C.[10]

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