mixture was stirred for 30 min at 25 °C. To the mixture was added a solution of 1.40 g (6.16 mM) of compound **15** in 5 mL of THF at -20 °C. The mixture was stirred for 1 h at -20 °C and partitioned between AcOEt and 2 N HCl. The organic solution was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified on silica gel [eluted with toluene–AcOEt (9:1)–(4:1)], which gave 750 mg (39.1%) of the desired acid **9** as a colorless gum. ^1H NMR ($CDCl_3$): δ 1.30–1.85 (m, 4 H), 1.85–2.20 (m, 4 H), 2.33 (t, J = 7 Hz, 2 H), 2.93 (q, J = 7 Hz, 2 H), 5.11 (t, J = 7 Hz, 1 H), 5.20–5.45 (m, 2 H), 7.40–7.98 (m, 5 H), 9.10 (br s, 1 H).

9-[(Phenylsulfonyl)amino]nonanoic Acid (6). A mixture of 50 mg of 10% palladium carbon and 311 mg (1 mM) of compound **9** in 20 mL of methanol was stirred for 1 h under hydrogen atmosphere (1 atm). After filtration, the filtrate was concentrated in vacuo to give 300 mg (95.8%) of compound **6** as colorless pillars.

4-[(Phenylsulfonyl)amino]butyric Acid (1). To a solution of 0.5 g of γ-aminobutyric acid in 10 mL of 1 N NaOH and 5 mL of water was added a solution of 1.7 mL of phenylsulfonyl chloride in 1.5 mL of dioxane at room temperature. The mixture was stirred for 2 h at the same temperature, partitioned between ether and water. The aqueous solution was acidified with 2 N HCl and extracted with AcOEt. The organic solution was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The crystalline residue was recrystallized from a mixture of CH_2Cl_2 and *n*-hexane, which gave 1.1 g (90%) of compound **1** as colorless needles. Compounds **2–5**, **7**, and **8** were synthesized from $H_2N(CH_2)_nCO_2H$ (n = 4–7, 10, and 11) by the same method, respectively. For **1–9**, the physical properties and characteristic infrared frequencies are given in Tables II and III, respectively.

Biology. Tests, using methods described previously,[3,15] gave the results presented in Table II.

Acknowledgment. We are grateful to Dr. M. Narisada, the Director of Shionogi Research Laboratories, Dr. H. Arita, and Dr. K. Ezumi for their helpful discussions and to Dr. K. Hanasaki and Mrs. A. Terawaki for measurements of IC_{50} values of inhibitory activities.

Naphtho and Benzo Analogues of the κ Opioid Agonist *trans*-(±)-3,4-Dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide

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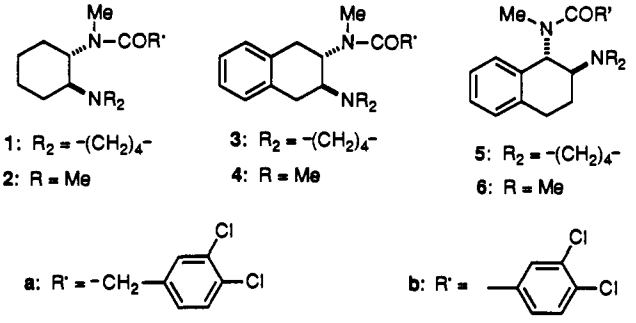
Further elaboration on the structure–activity relationships in our U-50,488 series has revealed that benzologation of this cyclohexane-1,2-diamine derivative provides compounds which either maintain the interaction with the κ receptor (e.g. compounds **3a** and **5a** in the phenylacetamido series) or eliminate the μ receptor mediated analgesia (e.g. compounds **3–6** in the benzamido series). Naphthologation also caused the elimination of μ receptor mediated analgesia (e.g. compounds **17a** and **17b**).

The disclosure[1] of a selective agonist (**1**, U-50,488) for the κ receptor in the central nervous system has triggered significant activity in the preparation of additional agonists and in the search for antagonists in this series.[2] For example, different acyl derivatives of the basic *trans*-1,2-cyclohexanediamine template have been prepared.[3] The recent disclosure[4] of 4,5- (**3a**) and 5,6- (**5a**) benzo derivatives of **1a** has stimulated us to report our efforts in this area.



Chemistry

All the compounds described below are racemic mixtures.

The benzo derivatives **3–6** were prepared by the same general route as that used for U-50,488 starting from the appropriate dihydronaphthalene as shown in Scheme I, routes A and B. Since it had been shown earlier that the 3,4-dichlorobenzamide analogue of **1a** (**2b**) was a μ agonist, these analogues (**3b–6b**) were prepared in addition to the 3,4-dichlorophenylacetamides (**3a,b**).

Finally, naphthologues **17a** and **17b** were prepared as shown in Scheme I, route C. The requisite starting material, 1,4-dihydroanthracene, was prepared as previously described[6] from acid treatment of the Diels–Alder adduct of 1,4-epoxy-1,4-dihydronaphthalene and 1,3-butadiene.

The chemistry outlined in Scheme I is straightforward except that it was found that 2,3-epoxytetralin was quite susceptible to polymerization in the absence of solvent. Thus, this intermediate was not isolated but treated di-

†The Upjohn Co., Kalamazoo, MI.

(1) Szmuszkovicz, J.; VonVoigtlander, P. F. *J. Med. Chem.* **1982**, *25*, 1125 (US Pat. 4,098,904, US Appl. No. 741,467, filed Nov. 12, 1976; *Chem. Abstr.* **1978**, *89*, 146632s. US Pat. 4,145,435; *Chem. Abstr.* **1979**, *91*, 39003g). VonVoigtlander, P. F.; Lahti, R. A.; Ludens, J. H. *J. Pharmacol. Exp. Ther.* **1983**, *224*, 7.
(2) For leading references, see: (a) de Costa, B. R.; Brown, W. D.; Hellewell, S. B.; George, C.; Rothman, R. B.; Reid, A. A.; Walker, J. M.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **1989**, *32*, 1996. (b) Halfpenny, P. R.; Horwell, D. C.; Hughes, J.; Hunter, J. C.; Rees, D. C. *J. Med. Chem.* **1990**, *33*, 286.
(3) Halfpenny, P. R.; Hill, R. G.; Horwell, D. C.; Hughes, J.; Hunter, J. C.; Johnson, S.; Rees, D. C. *J. Med. Chem.* **1989**, *32*, 1620.
(4) Pennev, P.; Rajagopalan, P.; Scribner, R. M. Eur. Pat. Appl. EP 260,555; *Chem. Abstr.* **1989**, *110*, 8036b.
(5) Sugihara, H.; Ukawa, K.; Miyake, A.; Itoh, K.; Sanno, Y. *Chem. Pharm. Bull.* **1978**, *26*, 394.
(6) Muller, P.; Rey, M. *Helv. Chim. Acta* **1982**, *65*, 1157.
(7) Simon, E. J.; Hiller, J. M.; Edelman, I. *Proc. Nat. Acad. Sci. U.S.A.* **1973**, *70*, 1947.
(8) Lahti, R. A.; Mickelson, M. M.; McCall, John M.; Von Voigtlander, P. F. *Eur. J. Pharm.* **1985**, *109*, 281.

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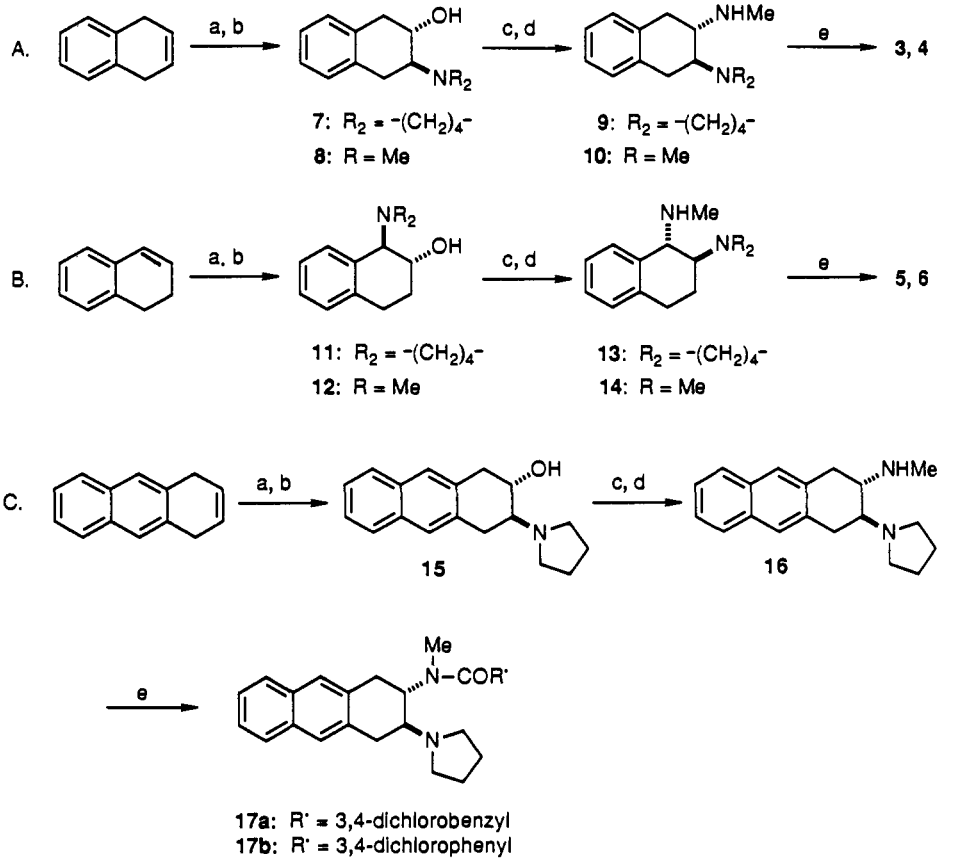
Scheme I[a]



[a] (a) *m*CPBA, $CHCl_3$, 0 °C; (b) C_4H_8NH, 95 °C; 18 h; (c) CH_3SO_2Cl, NEt_3, CH_2Cl_2; (d) CH_3NH_2, 70 °C, 16 h; (e) 3,4-dichlorophenylacetic acid, CDI, THF or 3,4-dichlorobenzoic acid, NEt_3, ether.

rectly with pyrrolidine after removal of any residual *m*-chloroperoxybenzoic acid from the epoxidation mixture. This procedure was also followed for the preparation of **15**.

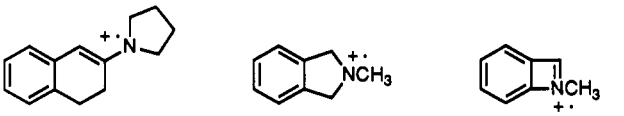
Results and Discussion

In the case of compounds **5** and **6** it was important to establish the regiochemistry to be as shown. The structure of **5a** had been proposed previously without proof.[4] There are two steps in Scheme I which could produce regioisomers; step b in which the unsymmetrical epoxide reacts with pyrrolidine and step d in which an unsymmetrical aziridinium salt is formed and reacts with methylamine. It had been established earlier by Sugihara and co-workers[5] that 1,2-epoxytetralin reacts with primary amines exclusively at the 1-position on the basis of the absence of a signal in the NMR spectra of these compounds which was characteristic of the PhC*H*OH proton. In the present case, treatment of this epoxide with either pyrrolidine or dimethylamine leads to exclusive attack of the amines at the 1-position also, as clearly shown by the NMR spectra of the amino alcohols.

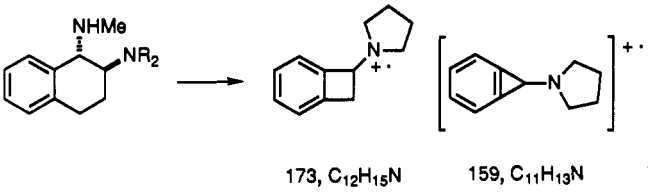
The absorptions of the methine hydrogens α to the hetero atoms appear at δ 3.94 (m, C_2) and 3.78 (d, C_1) for **11** and at δ 3.90 and 3.63 for the dimethylamino analogue **12**. If the alternative regioisomers were present, absorptions at $\delta \sim 5.0$ (C_1) and 2.5–3.0 (C_2) would be expected.

Unfortunately, the ^1H NMR spectra of the diamines (**13** and **14**) are not so diagnostic. It is clear that only one diastereoisomer is present, but which one could not be determined. However, the ^1H NMR spectra of amides **5** and **6** are consistent with the assigned structure (see the Experimental Section). The mass spectrum (EI) of **13** allowed assignment of the regiochemistry shown. It showed the expected molecular ion peak at *m/e* 230. From analysis of the mass spectrum shown in Scheme II the following conclusions may be drawn.

Scheme II



Scheme III



(1) The ion of *m/e* 199 is formed by loss of methylamine. (2) The ion of *m/e* 133 is a product arising from cleavage of the cyclohexyl ring. The presence of this fragment indicates that the methylamine group is located at C_1 as shown in **13**. This conclusion is also supported by the ion present at *m/e* 118. Further support for this assignment stems from the absence of fragment ions at *m/e* 173 and 159 which would be expected fragment ions for cleavage of the alternative regioisomer (Scheme III).

These conclusions are also consistent with the fact that Sugihara et al.[5] showed that hydrolysis of 1,2-iminotetralin occurred exclusively at carbon-1; since the transition state for attack of amine on the aziridinium intermediate in step d is likely to have considerable S_N1 character, it seems justified to expect the second amine also to attack at the

1-position. This sequence provides an interesting way to control regiochemistry through the order in which the amines are introduced.

Biological Results

The data in Table I delineate the analgesic activity of the subject compounds in antinociceptive tests in mice and also ligand-binding results. The in vivo tests involve heat (tail flick), pressure (tail pinch), and chemical irritation (HCl writhing) stimulus modalities. In each of these in vivo tests, **3a** and **5a** (in the phenylacetamido series) were active and displayed a potency essentially identical with that previously reported[1] for **1a**. This suggests that benzo substitution of the cyclohexyl ring of **1a** is tolerated by the κ opioid receptor. Compound **6a** is less active because of the preferred pyrrolidine to dimethylamine substitution. The larger naphtho substitution is not tolerated in vivo by the κ opioid receptor as it leads to an inactive compound, **17a**. The 3,4-dichlorobenzoyl analogues of **1a**, particularly those containing a dimethylamino group (i.e. **2b**) rather than a pyrrolidinyl group, have been shown[1] to be potent μ agonists in vivo (e.g. U-47,700). In the series reported here, this activity was apparently totally diminished in vivo by the benzo and naphtho substitutions of the cyclohexyl ring (Table I). But, in vitro, **4b** retains high affinity for μ binding sites. This affinity is apparently not related to μ antagonist activity as none of the compounds in Table I demonstrated the antagonism of morphine-induced analgesia[1] at 100/kg (data not shown).

Experimental Section

General Procedures. ^{1}H NMR spectra were obtained on a 200-MHz Magnachem, a 300-MHz GN-300, or a Bruker AM-500 spectrometer and were recorded on $CDCl_3$ solutions. Proton chemical shifts are given in ppm relative to Me_4Si (=0 ppm, ^{1}H). IR spectra were recorded on a Perkin-Elmer infrared spectrometer. Melting points were measured using a Thomas-Hoover Unimelt apparatus and are uncorrected. Mass spectra were obtained on MAT CH-5-DF (FAB) and Finnigan 8230 B (EI) mass spectrometers. Elemental analyses were performed by the Upjohn Company and M-H-W Laboratories, Phoenix, AZ, and are within 0.4% of the theoretical values.

The following chemicals were obtained from commercial sources and were used without further purification: methylamine, pyrrolidine, methanesulfonyl chloride, 3-chloroperoxybenzoic acid (80–85%), triethylamine, 3,4-dichlorobenzoyl chloride, 1,4-epoxy-1,4-dihydronaphthalene, 1,2-dihydronaphthalene (80%), 1,1′-carbonyldiimidazole, 3,4-dichlorophenylacetic acid (Aldrich), diethyl ether (Fisher, reagent ACS, anhydrous), methylene chloride (Fisher, certified ACS). Tetrahydrofuran (Fisher, certified) was purified by refluxing over sodium under nitrogen followed by distillation.

Preparation of Amino Alcohols. *trans*-1-Pyrrolidinyl-2-hydroxy-1,2,3,4-tetrahydronaphthalene (11). 1,2-Dihydronaphthalene (3.91 g, 30.0 mmol) was dissolved in 100 mL of $CHCl_3$ and cooled to 0 °C. 3-Chloroperoxybenzoic acid (8.50 g, 42.0 mmol) was then added in portions to the cooled solution. The resulting white suspension was stirred at ambient temperature for 35 min. The reaction mixture was then washed with 5% aqueous K_2CO_3 (3 × 25 mL), dried over $MgSO_4$, filtered, and evaporated, providing a brown oil. The crude epoxide was immediately combined with pyrrolidine (5.00 mL, 59.9 mmol) and heated to 95 °C for 16 h. The resulting brown oil was dissolved in 100 mL of ether and washed with saturated aqueous Na_2CO_3 (50 mL). The ether layer was then extracted with 10% HCl (2 × 50 mL). The acidic portion was neutralized with solid Na_2CO_3 and extracted with ether (2 × 50 mL). Drying the ether solution over $MgSO_4$, filtering, and concentration provided 4.60 g (71%) of 11 as a red oil: ^{1}H NMR (500 MHz) δ 1.6–1.8 (m, 6 H, 3 × C*H*$_2$), 2.28 (m, 1 H, benzylic C*H*), 2.8–2.9 (m, 6 H, OH, benzylic C*H* and 2 × C*H*$_2$N), 3.78 (d, J = 7.6 Hz, 1 H, C*H*N), 3.94 (m, J = 9.2, 3.5, 7.6 Hz, 1 H, C*H*OH), 7.15 (m, 3 H, Ar*H*), 7.20 (d, J = 9 Hz, 1 H, Ar*H*); IR ($CDCl_3$) 3400 (br, OH) cm^{-1}; MS (EI) m/e 217 (M^+), 172 (100), 158. This coupling constant (7.6 Hz) is large enough to strongly suggest that the stereochemistry of positions 1 and 2 is trans. HCl salt: mp 148–149 °C. Anal. ($C_{14}H_{20}NOCl$) C, H, N, Cl.

***trans*-2-Hydroxy-3-pyrrolidinyl-1,2,3,4-tetrahydronaphthalene** (7). By the same procedure, 1.30 g (0.799 mmol) of 80% 1,4-dihydronaphthalene in 12 mL of $CHCl_3$ was treated with 2.83 g (14.0 mmol) of 3-chloroperoxybenzoic acid and 2.00 mL (24.0 mmol) of pyrrolidine to yield 0.840 g (48%) of **7**. Half of the pyrrolidine was added before concentration of the epoxide on the rotary evaporator to suppress polymerization: ^{1}H NMR (200 MHz) δ 1.80 (br s, 4 H, 2 × C*H*$_2$), 2.75 (m, 7 H, 3 × C*H*$_2$, 1 × C*H*), 2.87 (s, 1 H, O*H*), 2.99 (m, 1 H, C*H*), 3.30 (dd, J = 6, 16 Hz, 1 H, C*H*N), 3.82 (m, 1 H, C*H*OH), 7.15 (s, 4 H, Ar*H*); IR ($CDCl_3$) 3420 (br, OH) cm^{-1}; MS (EI) m/e 217 (M^+). HCl salt: mp 158–159 °C. Anal. ($C_{14}H_{20}NOCl$) C, H, N, Cl.

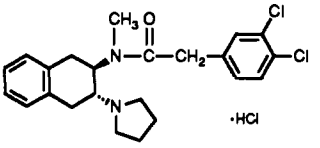
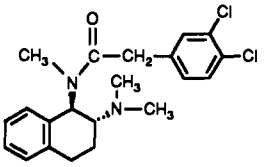
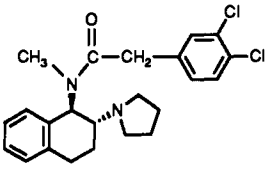
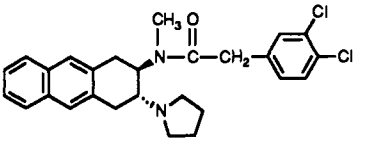
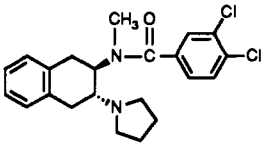
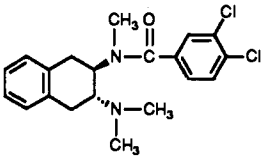
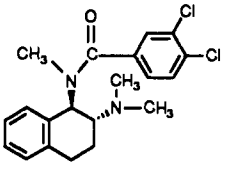
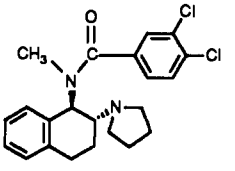
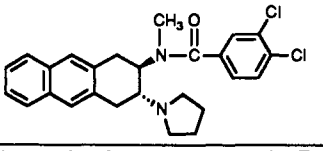
***trans*-2-Hydroxy-1-(dimethylamino)-1,2,3,4-tetrahydronaphthalene** (12). By the same procedure, 1,2-dihydronaphthalene (3.91 g, 30.0 mmol), dissolved in 100 mL of $CHCl_3$, was treated with 8.50 g (42.0 mmol) of 3-chloroperoxybenzoic acid and 60 mL (533 mmol) of 40% aqueous dimethylamine and heated to 40 °C for 3 h. Isolation as above gave 5.57 g (97%) of **12** as a tan solid: mp 36–38 °C; ^{1}H NMR (200 MHz) δ 1.71–1.84 (m, 1 H, C*H*), 2.06–2.18 (m, 1 H, C*H*), 2.45 (s, 6 H, N(C*H*$_3$)$_2$), 2.76 (m, 2 H, benzylic C*H*$_2$), 3.63 (d, J = 8 Hz, 1 H, C*H*NMe$_2$), 3.70 (s, 1 H, O*H*), 3.85-3.95 (m, 1 H, C*H*OH), 7.04–7.12 (m, 3 H, Ar*H*), 7.36 (dd, J = 4, 6 Hz, 1 H, Ar*H*); IR (neat) 3405 (br, OH) cm^{-1}; MS (EI) m/e 191 (M^+). HCl salt: mp 176–178 °C. Anal. ($C_{12}H_{18}NOCl$) C, H, N, Cl.

***trans*-2-Hydroxy-3-(dimethylamino)-1,2,3,4-tetrahydronaphthalene** (8). Similarly 1,4-dihydronaphthalene (3.25 g, 20.0 mmol), dissolved in 24 mL of $CHCl_3$, was treated with 6.02 g (28.0 mmol) of 3-chloroperoxybenzoic acid and 30.0 mL (267 mmol) of 40% aqueous dimethylamine to produce 1.30 g (34%) of **8** as a red oil (Again in the case of this epoxide half of the dimethylamine solution was added before concentration of the epoxidation reaction product.): ^{1}H NMR (200 MHz) δ 2.36 (s, 6 H, N(C*H*$_3$)$_2$), 2.80 (m, 4 H, C*H*$_2$, C*H*N, C*H*), 3.27 (dd, J = 6, 16 Hz, 1 H, C*H*), 3.80 (m, 1 H, OC*H*), 7.10 (s, 4 H, Ar*H*); IR (neat) 3415 (br, OH) cm^{-1}; MS (EI) m/e 191 (M^+), 128 (100). HCl salt: mp 176–178 °C. Anal. ($C_{12}H_{18}NOCl$) C, H, N, Cl.

***trans*-2-Hydroxy-3-pyrrolidinyl-1,2,3,4-tetrahydroanthracene** (15). Similarly, 1.00 g (5.55 mmol) of 1,4-dihydroanthracene[6] in 10 mL of $CHCl_3$ was treated with 1.34 g (6.41 mmol) of 3-chloroperoxybenzoic acid and then pyrrolidine (4.00 mL, 47.9 mmol) (2 mL each before and after concentration of the epoxide) to give 1.25 g (85%) of **15** as a tan solid. In this case purification by acidic extraction was omitted. For analytical purposes **15** was recrystallized from ethanol: mp 113–113.5 °C; ^{1}H NMR (200 MHz) δ 1.83 (br s, 4 H, 2 × C*H*$_2$), 2.77–3.04 (m, 8 H, 2 × NC*H*$_2$, C*H*$_2$Ar, C*H*N, C*H*), 3.5 (dd, J = 6, 16 Hz, 1 H, C*H*), 3.93 (m, 1 H, C*H*OH), 4.10 (br s, 1 H, O*H*), 7.38 (m, 2 H, Ar*H*), 7.58 (m, 2 H, Ar*H*), 7.72 (m, 2 H, Ar*H*); IR (KBr) 3200 (br, OH) cm^{-1}; MS (EI) m/e 267 (M^+). Anal. ($C_{18}H_{21}NO$) C, H, N.

Preparation of Diamines. *trans*-2-Pyrrolidinyl-1-(methylamino)-1,2,3,4-tetrahydronaphthalene (13). Compound 11 (4.81 g, 22.2 mmol) was diluted with 25 mL of CH_2Cl_2 and cooled to 0 °C under N_2. Triethylamine (2.46 g, 24.4 mmol) was added with a syringe. Methanesulfonyl chloride (3.39 mL, 24.4 mmol) was diluted with 4 mL of CH_2Cl_2 and added dropwise with a syringe over 5 min. The solution was stirred for 1.5 h at 0 °C, and then the solvent was removed on a rotary evaporator at room temperature. The resulting brown residue was transferred to a pressure vessel with 15.0 mL (339 mmol) of anhydrous methylamine. The pressure reactor was sealed and heated to 70 °C (external) for 18 h. After cooling to room temperature, the brown reaction mixture was dissolved in 100 mL of ether and washed with saturated KOH (1 × 50 mL) and brine (1 × 50 mL). Drying the ether layer over $MgSO_4$, filtering, and evaporation of the solvent provided 4.20 g (82%) of 13 as a brown oil: ^{1}H NMR (200 MHz) δ 1.72 (m, 5 H, C*H*$_2$), 2.0–2.15 (m, 1 H, C*H*), 2.48 (s, 3 H, NC*H*$_3$), 2.55–2.70 (m, 6 H, C*H*$_2$), 2.81–2.95 (m, 1 H, C*H*N), 3.67 (m, 1 H, C*H*N), 7.1–7.2 (m, 3 H, Ar*H*), 7.35 (m, 1 H, Ar*H*); IR (film) 3330 (w, NH) cm^{-1}; MS (EI) m/e 230 (M^+). The spectral overlap in the region δ 2.6–3.0 did not allow stereochemical assignment.

Table I. Analgesic Activities

	compound	analgesic assay (ED_{50}, mg/kg sc)[a] flick	pinch	writhe	μ binding: [^{3}H]etorphine[7] K_i, nM	κ binding: [^{3}H]U-69,593 IC_{50}, nM[8]
U-47,700[b]		0.2	0.22	0.16	52	not tested
U-50,488		2.5	2.5	2.5	>1000	5.4
3a		2	2	1.1	>1000	5.2
6a		28	28	25	>1000	11.7
5a		2	0.5	0.8	>1000	7.3
17a		>100	>100	>100	>1000	144.9
3b		>100	>100	>100	374	29
4b		>100	>100	>100	21	55.5
6b		>100	>100	>100	505	2200
5b		>100	>100	>100	>1000	368
17b		>100	>100	71	>1000	84.9

[a] 95% Confidence intervals of these calculated ED_{50} values are generally 0.5–2 × ED_{50}. Six mice were tested at each dose. [b] *trans*-2-(Dimethylamino)-1-(*N*-methyl-3′,4′-dichlorobenzamido)cyclohexane.

***trans*-1-(Methylamino)-2-(dimethylamino)-1,2,3,4-tetrahydronaphthalene (14).** By the same procedure 1.76 g (9.20 mmol) of **12** in 25 mL of CH_2Cl_2 was treated successively with 1.41 mL (10.1 mmol) of triethylamine, 0.780 mL (10.1 mmol) of methanesulfonyl chloride, and 10.0 mL (226 mmol) of methylamine to give 1.68 g (90%) of **14** as a brown oil: ^{1}H NMR (200 MHz) δ 1.67 (m, 1 H), 2.05 (m, 1 H), 2.31 (s, 6 H, $N(CH_3)_2$), 2.34 (s, 3 H, NCH_3), 2.28–2.40 (m, 1 H), 2.70 (m, 3 H), 3.78 (d, J = 10 Hz, 1 H, MeHNC*H*), 7.20 (m, 3 H, Ar*H*), 7.55 (m, 1 H, Ar*H*); IR (film) 3320 (NH) cm^{-1}; MS (EI) *m/e* (relative intensity) 204 (M^+, weak), 173 (100), 146 (28), 129 (53), 118 (81).

***trans*-2-Pyrrolidinyl-3-(methylamino)-1,2,3,4-tetrahydronaphthalene (9).** By the same procedure 1.70 g (7.83 mmol) of **7** in 25 mL of CH_2Cl_2 was treated successively with 1.20 mL (8.61 mmol) of triethylamine, 0.667 mL (8.61 mmol) of methanesulfonyl chloride, and 15.0 mL (339 mmol) of methylamine to provide 1.58

g (88%) of **9** as a red oil: ^{1}H NMR (200 MHz) δ 1.76 (m, 4 H, 2 × CH_2), 2.2 (br s, 1 H, NH), 2.49 (s, 3 H, NCH_3), 2.64 (m, 6 H, 2 × NCH_2, CH_2), 2.7–2.8 (m, 1 H, CHN), 2.86 (m, 2 H, CHN, CH), 3.15 (dd, J = 5, 16 Hz, 1 H, CH), 7.00 (s, 4 H, ArH); IR (film) 3330 (w, NH) cm^{-1}; HRMS (EI) calcd for $C_{15}H_{22}N_2$: 230.1783, found 230.1793.

***trans*-2-(Dimethylamino)-3-(methylamino)-1,2,3,4-tetrahydronaphthalene (10).** By the same procedure 1.02 g (5.33 mmol) of **8** in 25 mL of CH_2Cl_2 was treated successively with triethylamine (0.764 mL, 5.50 mmol), methanesulfonyl chloride (0.639 mL, 8.26 mmol), and methylamine (10.0 mL, 226 mmol) to give 0.97 g (95%) of **10** as a red oil: ^{1}H NMR (200 MHz) δ 2.30 (s, 6 H, N(CH_3)$_2$), 2.50 (s, 3 H, NCH_3), 2.60–2.67 (m, 2 H, CH_2Ar), 2.74–2.82 (m, 3 H, CH_2Ar, CHN), 3.22 (dd, J = 11, 3 Hz, 1 H, CHN), 7.10 (s, 4 H, ArH); IR (film) 3322 (NH) cm^{-1}; HRMS (EI) calcd for $C_{13}H_{20}N_2$ 204.1626, found 204.1634.

***trans*-2-Pyrrolidinyl-3-(methylamino)-1,2,3,4-tetrahydroanthracene (16).** By the same procedure 0.881 g (3.29 mmol) of **15** in 10 mL of CH_2Cl_2 was treated successively with 0.504 mL (3.62 mmol) of triethylamine, 0.281 mL (3.63 mmol) of methanesulfonyl chloride, and 10.0 mL (226 mmol) of methylamine to give 0.943 g (~100%) of a yellow oil. Crystallization from hexane gave 680 mg (73%) of **16** as a yellow solid: mp 99 °C; ^{1}H NMR (200 MHz) δ 1.78 (br s, 4 H, 2 × CH_2), 1.85 (s, 1 H, NH), 2.51 (s, 3 H, NCH_3), 2.67 (m, 4 H, 2 × NCH_2), 2.7–3.3 (m, 6 H, 2 × CH_2Ar, MeNHCH, NCH), 7.37 (m, 2 H, ArH), 7.58 (br s, 2 H, ArH), 7.72 (m, 2 H, ArH); IR (KBr) 3310 (NH) cm^{-1}; MS (EI) m/e 280 (M$^+$). Anal. ($C_{19}H_{24}N_2$) C, H, N.

Preparation of Monoacyldiamines. *trans*-2-(Dimethylamino)-1-(*N*-methyl-3′,4′-dichlorophenylacetamido)-1,2,3,4-tetrahydronaphthalene (6a). 3,4-Dichlorophenylacetic acid (1.03 g, 5.00 mmol) and 1,1′-carbonyldiimidazole (0.827 g, 5.10 mmol) were combined in 25 mL of THF and stirred at ambient temperature for 2 h. Compound **14** (1.02 g, 5.00 mmol) was then diluted with 5 mL of THF and added dropwise with a syringe. The brown solution was stirred for 20 h at room temperature. The solvent was then evaporated, and the residue was dissolved in 150 mL of ether and washed with saturated aqueous Na_2CO_3 (2 × 50 mL). The ether layer was then extracted twice with 50 mL of 10% HCl. The acidic portion was neutralized with solid Na_2CO_3 and extracted twice with 50 mL of ether. Drying of the ether extracts over $MgSO_4$, filtering, and evaporation to dryness provided 0.990 g of **6a** as a brown oil (51%): ^{1}H NMR (200 MHz) (mixture of two conformers) δ 1.6–1.85 (m, 1 H, CH), 2.1–2.2 (m, 1 H, CH), 2.38–2.39 (2 s, total of 6 H, N(CH_3)$_2$), 2.60 (m, 1 H, CHN), 2.70 (s, 3 H, NCH_3), 2.75–2.95 (m, 3 H, CH_2, CHN), 3.8 (d, J = 15 Hz, 1 H, CH_2Ar), 3.9 (d, J = 15 Hz, 1 H, CH_2Ar), 4.95 and 6.05 (2 d, J = 9 Hz, total of 1 H, CHN), 7.05–7.25 (m, 5 H, ArH), 7.4 and 7.45 (2 s, total of 1 H, ArH), 7.53 (d, J = 3 Hz, 1 H, ArH); IR ($CDCl_3$) 1639 (s, CO) cm^{-1}; MS (CI, isobutane) m/e 391 (M + H)$^+$. HCl salt: mp 218–220 °C. Anal. ($C_{21}H_{25}N_2OCl_3$) C, H, N, Cl.

***trans*-2-Pyrrolidinyl-1-(*N*-methyl-3′,4′-dichlorophenylacetamido)-1,2,3,4-tetrahydronaphthalene (5a).** In the same manner, 1.03 g (5.00 mmol) of 3,4-dichlorophenylacetic acid, 0.827 g (5.10 mmol) of 1,1′-carbonyldiimidazole, and 1.15 g (5.00 mmol) of **13** in 35 mL of THF gave a brown oil which was chromatographed on silica gel using $CHCl_3$/MeOH/NH_4OH (95:4:1) as eluent providing 1.50 g (72%) of **5a** as a yellow brown oil: ^{1}H NMR (200 MHz) (mixture of conformers in a ratio of 3:1) δ 1.71 (m, 5 H), 2.03 and 2.09 (2 m, total of 1 H, CH), 2.55–2.65 (m, 3 H, CH_2 and CH), 2.60 and 2.63 (2 s, total of 3 H, NCH_3), 2.75–3.10 (m, 4 H, 2 × CH_2), 3.72 (d, J = 15 Hz, 1 H, CH_2Ar), 3.84 (d, J = 13 Hz, 1 H, CH_2Ar), 4.97 and 5.95 (2 d, J = 10 Hz, total of 1 H, CHN), 7.02–7.20 (m, 5 H, ArH), 7.34 and 7.40 (2 s, total of 1 H, ArH), 7.43 (d, J = 2.5 Hz, 1 H, ArH); IR ($CDCl_3$) 1643 (s, CO) cm^{-1}. HCl salt: mp 228–230 °C. Anal. ($C_{23}H_{27}N_2OCl_3$) C, H, N, Cl.

The signals at δ 4.97 and 5.95 are assigned to the methine H of the amide group at C_1 whereas the same signal in the alternative regioisomer would be expected at ~δ 4.0. The methine H at C_2 is obscured by overlapping absorptions but must appear at δ 3.1 or further upfield, while that signal in the alternative regioisomer would be expected in the region δ ~4.0–5.0 (cf. the analogous methine H in compound **17a** below: δ 5.15). Note the similarity to the methine H of the amide group of **6a** (δ ~4.95 and 6.05). The spectral overlap in the region 2.5 to 3.0 δ did not allow stereochemical assignment.

***trans*-2-Pyrrolidinyl-3-(*N*-methyl-3′,4′-dichlorophenylacetamido)-1,2,3,4-tetrahydroanthracene (17).** Diamine **16** (100 mg, 0.357 mmol) was converted to compound **17a** as described above except that the purification step involving extraction of the product into 10% HCl was omitted. The yellow foam (174 mg, ca. 100%) thus obtained was recrystallized from benzene/pentane to give 151 mg (90%) of **17a** as a yellow crystalline solid: mp 77 °C; ^{1}H NMR (200 MHz) δ 1.75 (br s, 4 H, 2 × CH_2), 2.64 (br s, 4 H, 2 × NCH_2), 2.84 (s, 3 H, NCH_3), 2.90–3.30 (m, 5 H, NCH and 2 × ArCH_2), 3.70 (s, 2 H, COCH_2), 5.15 (br s, 1 H, CONCH), 7.15 (m, 1 H, ArH), 7.39 (m, 4 H, ArH), 7.57 (m, 2 H, ArH), 7.73 (br s, 2 H, ArH); IR (film) 1640 (CO) cm^{-1}; MS (FAB) m/e 467 and 469 (M + H)$^+$. Anal. ($C_{27}H_{28}N_2OCl_2 \cdot {}^1/_2C_6H_6$) C, H, N, Cl.

***trans*-2-Pyrrolidinyl-3-(*N*-methyl-3′,4′-dichlorophenylacetamido)-1,2,3,4-tetrahydronaphthalene (3a).** In the same manner 3,4-dichlorophenylacetic acid (1.03 g , 5.00 mmol), 1,1′-carbonyldiimidazole (0.827 g, 5.10 mmol), and diamine **9** (1.15 g, 5.00 mmol) in 25 mL of dry THF provided 1.80 g (68%) of **3a** as a brown oil: ^{1}H NMR (200 MHz) δ 1.69 (br m, 4 H, 2 × CH_2), 2.59 (br m, 4 H, 2 × NCH_2), 2.86 (s, 3 H, NCH_3), 2.92 (m, 4 H, 2 × CH_2), 3.12 (m, 1 H, NCH), 3.70 (m, 2 H, CH_2), 5.00 (m, J = 7, 12 Hz, 1 H, NCH), 7.09 (m, 5 H, ArH), 7.37 (d, J = 9 Hz, 1 H, ArH), 7.38 (d, J = 9 Hz, 1 H, ArH); IR ($CDCl_3$) 1640 (CO) cm^{-1}; MS (EI) m/e 416 (M$^+$). HCl salt: mp 123–125 °C. Anal. ($C_{23}H_{26}N_2OCl_2 \cdot HCl \cdot H_2O$) C, H, N, Cl.

***trans*-2-Pyrrolidinyl-1-(*N*-methyl-3′,4′-dichlorobenzamido)-1,2,3,4-tetrahydronaphthalene (5b).** Compound **13** (1.84 g, 8.00 mmol) was diluted with 50 mL of ether and triethylamine (1.22 mL, 8.88 mmol) was added. 3,4-Dichlorobenzoyl chloride (1.67 g, 8.00 mmol) was dissolved in 15 mL of ether and added dropwise over 20 min with a dropping funnel. This brown suspension was stirred at room temperature for 18 h. The mixture was then diluted with 50 mL of ether and washed with saturated aqueous Na_2CO_3 (2 × 25 mL) and brine (25 mL). Drying over $MgSO_4$, filtering, and evaporation to dryness gave a tan solid which was crystallized from ethanol/ether to give 2.47 g of **5b** as a colorless solid (77%): mp 135–136 °C; ^{1}H NMR (300 MHz) (mixture of conformers in a ratio of 1:1) δ 1.45–1.9 (m, 6 H, 3 × CH_2), 2.15–2.25 (m, 1 H, CH), 2.45–2.55 (m, 1 H, CH), 2.62 and 2.74 (2 s, total of 3 H, NCH_3), 2.8–2.95 (m, 4 H, 2 × CH_2N), 3.05–3.22 (m, 1 H, CHN), 4.84 and 6.00 (2 d, J = 10 Hz, total of 1 H, CHN), 7.09–7.30 (m, 4 H, ArH), 7.40 (s, 1 H, ArH), 7.47 and 7.50 (2 d, J = 8 Hz, total of 1 H, ArH), 7.6 and 7.7 (2 s, total of 1 H, ArH); IR ($CDCl_3$) 1632 (s, CO) cm^{-1}; MS (FAB) m/e 403 (M + H)$^+$. Anal. ($C_{22}H_{24}N_2OCl_2$) C, H, N, Cl.

***trans*-2-Pyrrolidinyl-3-(*N*-methyl-3′,4′-dichlorobenzamido)-1,2,3,4-tetrahydroanthracene (17b).** Diamine **16** (300 mg, 1.07 mmol) was converted to compound **17b** as described above except that the purification step involving extraction of the product into 10% HCl was omitted. The crude oil (497 mg, ca. 100%) was crystallized from benzene/pentane to give 365 mg (75%) of **17b** as a yellow solid: mp 125–126 °C; ^{1}H NMR (200 MHz) δ 1.76 (br s, 4 H, 2 × CH_2), 2.85 br s, 3 H, NCH_3), 2.50–3.0 (m, 5 H, 2 × CH_2 and NCH), 3.16 (m, 4 H, 2 × NCH_2), 5.07 (br s, 1 H, CONMeCH), 7.38 (m, 4 H, ArH), 7.57 (br s, 3 H, ArH), 7.72 (m, 2 H, ArH); IR (film) 1630 (CO) cm^{-1}; MS (FAB) m/e 453, 455 (M + H)$^+$. Anal. ($C_{26}H_{26}N_2OCl_2$) C, H, N, Cl.

***trans*-2-Pyrrolidinyl-3-(*N*-methyl-3′,4′-dichlorobenzamido)-1,2,3,4-tetrahydronaphthalene (3b).** Diamine **9** (2.30 g, 10.0 mmol) was converted to compound **3b** as described above for **5b**. A brown oil was obtained and crystallized from ether/ethanol to give 1.80 g (45%) of **3b** as a white solid: mp 126–127 °C; ^{1}H NMR (200 MHz) δ 1.75 (br s, 4 H, 2 × CH_2), 2.6–2.8 (m, 4 H, 2 × CH_2), 3.0 (br s, 4 H, 2 × NCH_2), 3.2 (br 2, 3 H, NCH_3), 3.35 (m, 1 H, NCH), 5.10 (m, 1 H, NCH), 7.10 (s, 4 H, ArH), 7.35 (d, J = 10 Hz, 1 H, ArH), 7.55 (d, J = 10 Hz, 1 H, ArH), 7.65 (s, 1 H, ArH); IR ($CDCl_3$) 1625 (CO) cm^{-1}; MS (FAB) m/e 403 (M + H)$^+$. Anal. ($C_{22}H_{24}N_2OCl_2$) C, H, N, Cl.

***trans*-2-(Dimethylamino)-3-(*N*-methyl-3′,4′-dichlorobenzamido)-1,2,3,4-tetrahydronaphthalene (4b).** By the same method as described for the formation of **5b**, **10** (1.02 g, 5.00 mmol) was converted to the colorless solid dichlorobenzamide **4b** (0.600 g, 32%): mp 137–139 °C; ^{1}H NMR (200 MHz) δ 2.53 (br s, 6 H,

NMe_2), 2.60 and 2.63 (2 s, total of 3 H, NCH_3), 2.90 (m, 3 H, CH_2), 3.05 (m, 2 H, CH_2), 5.10 (m, 1 H, CHN), 7.12 (br s, 4 H, ArH), 7.27 (m, 1 H, ArH), 7.51 (m, 2 H, ArH); IR ($CDCl_3$) 1630 (s, CO) cm^{-1}; MS (EI) m/e 376 (M^+). Anal. ($C_{20}H_{22}N_2OCl_2$) C, H, N, Cl.

***trans*-2-(Dimethylamino)-1-(*N*-methyl-3',4'-dichlorobenzamido)-1,2,3,4-tetrahydronaphthalene (6b).** By the same method as described for **5b**, 14 (2.04 g, 10.0 mmol) was converted to 1.30 g (35%) of oily dichlorobenzamide **6b**. Crystals were obtained from ether: mp 134-136 °C; ^1H NMR (200 MHz) (mixture of two conformers, ca 3:2) δ 1.50 (m, 1 H), 1.85 (m, 1 H), 2.03-2.08 (m, 1 H), 2.06 and 2.39 (2 s, total of 6 H, NMe_2), 2.63 and 2.73 (2 s, total of 3 H, NCH_3), 2.80-2.95 (m, 2 H), 4.75 and 6.02 (2 d, J = 10 Hz, total of 1 H, CONCH), 7.15 (m, 4 H, ArH), 7.41 (m, 2 H, ArH), 7.65 (m, 1 H, ArH); IR ($CDCl_3$) 1640 (CO) cm^{-1}; MS (FAB) m/e 377, 379 $(M + H)^+$. Anal. ($C_{20}H_{22}N_2OCl_2$) C, H, N, Cl.

Biological Methods. Analgesic activities were determined in a battery of in vivo tests[1] utilizing female CF-1 mice (18-22 g). The test compounds were dissolved or suspended in 25% aqueous (carboxymethyl)cellulose and administered subcutaneously in a volume dose of 10 mL/kg. Fifteen minutes later the mice were subjected to the radiant heat tail flick, tail pinch, and HCl writhing (abdominal stretch) tests. Animals failing to respond to these nociceptive stimuli were scored as analgesic. Six mice were tested at each dose level and additional doses at 0.3 log intervals were tested if the previous dose resulted in >2/6 analgesic mice. ED_{50}'s were calculated by the method of Spearman and Karber for those compounds that were active at one or more doses.

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Tyrphostins. 2. Heterocyclic and α-Substituted Benzylidenemalononitrile Tyrphostins as Potent Inhibitors of EGF Receptor and ErbB2/neu Tyrosine Kinases†

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We have previously described a novel series of low molecular weight protein tyrosine kinase inhibitors which we named tyrphostins. The characteristic active pharmacophore of these compounds was the hydroxy-*cis*-benzylidenemalononitrile moiety. In this article we describe three novel groups of tyrphostins: (i) one group has the phenolic moiety of the *cis*-benzylidenemalononitrile replaced either with other substituted benzenes or with heteroaromatic rings, (ii) another is a series of conformationally constrained derivatives of hydroxy-*cis*-benzylidenemalononitriles in which the malononitrile moiety is fixed relative to the aromatic ring, and (iii) two groups of compounds in which the position trans to the benzenemalononitrile has been substituted by ketones and amides. Among the novel tyrphostins examined we found inhibitors which discriminate between the highly homologous EGF receptor kinase (HER1) and ErbB2/neu kinase (HER2). These findings may lead to selective tyrosine kinase blockers for the treatment of diseases in which ErbB2/neu is involved.

Introduction

In recent years it has become apparent that protein tyrosine kinases (PTKs) mediate proliferative signals as well as metabolic signals.[1] This realization promoted the hypothesis that PTK blockers (tyrphostins) can in principle become useful antiproliferative agents[2,3] and useful molecular tools to investigate signal transduction of PTKs. We have therefore synthesized low molecular weight PTK blockers[2-4] which we demonstrated to be competitive inhibitors of EGF receptor kinase and insulin receptor kinase[5] and showed them to be effective blockers of EGF-dependent proliferation.[2,3,6] We have developed tyrphostins which discriminate up to a factor of 10^3 in favor of EGF receptor kinase as compared to insulin receptor kinase. Furthermore, tyrphostins which were found to be effective in inhibiting EGF receptor kinase in vitro and EGF-dependent proliferation were indeed shown to inhibit the EGF-induced tyrosine phosphorylation of intracellular proteins including phospholipase C[7] and therefore EGF-induced phosphotidylinositol bisphosphate (PIP_2) breakdown.[8] These findings encouraged us to examine whether EGF receptor selective tyrphostins can inhibit EGF-dependent proliferation of human keratinocytes. Indeed, we can demonstrate strong inhibitory effects of EGF receptor directed tyrphostins on the EGF-induced proliferation of normal human keratinocytes, of SCL-1 carcinoma, and of guinea pig epidermal cells in organ culture.[9] In this report we examine novel tyrphostins which deviate in structure from the classical BMN moiety. We prepared three classes of novel tyrphostins: (i) those in which the aromatic nucleus has been replaced by a heterocyclic ring, (ii) those in which the *cis*-cyano group was conformationally con-

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† Abbreviations: EGF, epidermal growth factor; PDGF, platelet-derived growth factor; PolyGAT, copoly-Glu_6Ala_3Tyr (random); BMN, benzylidenemalononitrile; PTK, protein tyrosine kinase.

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