Urea and 2-Imidazolidone Derivatives of the Muscarinic Agents Oxotremorine and *N*-Methyl-*N*-(1-methyl-4-pyrrolidino-2-butynyl)acetamide

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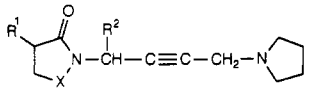
Some urea and 2-imidazolidone analogues of the muscarinic agents oxotremorine (1) and *N*-methyl-*N*-(1-methyl-4-pyrrolidino-2-butynyl)acetamide [10; BM-5] have been synthesized and assayed for muscarinic and antimuscarinic activity on the isolated guinea pig ileum. The new compounds (15–24) were found to be muscarinic agonists, partial agonists, or antagonists. The compounds were also tested for in vitro receptor binding to homogenates of the rat cerebral cortex using the muscarinic antagonist [^{3}H]-3-quinuclidinyl benzilate ([^{3}H]QNB) as the ligand. They were found to be less potent than 1 in this assay. On the guinea pig ileum, the *N*-3-methyl substituted imidazolidone analogue **20** was the most potent agonist of the new compounds studied; **20** was 5-fold more potent in inducing contractions of the ileum and had 4-fold higher affinity for ileal muscarinic receptors than the 3-methyl substituted 2-pyrrolidone **6**. However, the N-3-unsubstituted urea and imidazolidone derivatives **15** and **19** were several-fold less potent than the parent acetamide *N*-methyl-*N*-(4-pyrrolidino-2-butynyl)acetamide [9; UH-5] and **1**, respectively. The urea analogue (**16**) of the partial muscarinic agonist **10** was devoid of intrinsic activity and displayed 3-fold lower affinity than **10** for ileal muscarinic receptors.

Introduction

Most methyl and phenyl substitutions in the potent muscarinic agonist oxotremorine (**1**)[1] have resulted in muscarinic antagonists.[2,3] Among the more potent of these antimuscarinic agents are the 5-methyl substituted pyrrolidone **2** and the C1-methyl substituted derivative **8**.[2b] Compound **2** shows 12-fold higher affinity for ileal M_3[4,5] muscarinic receptors than **1**. In addition, **2** behaves as a potent tremorolytic[6] and antihypertensive[7] agent by antagonizing central muscarinic receptors. It is noteworthy that the (*R*)-enantiomer of **2** is 105-fold more potent as an antagonist at ganglionic M_1 muscarinic receptors than at M_3 receptors in vitro.[8]

In a recent study the methylene group in the 5-position of the pyrrolidone ring of **1** was replaced by, e.g., NH, *N*-formyl, or *N*-acetyl groups, giving the pyrazolidin-3-one derivatives **3**, **4**, and **5**, respectively.[8] The N-1 unsubstituted pyrazolidone analogue **3** was an agonist at ileal M_3 and at ganglionic M_1 muscarinic receptors with lower (30- and 50-fold, respectively) potency than **1**. As observed for **1**, compound **3** displayed low M_1/M_3 receptor subtype selectivity in vitro. However, the *N*-formyl derivative **4**, which was an antagonist, showed approximately 500-fold higher affinity for ganglionic M_1 receptors than for ileal M_3 receptors. The *N*-acetyl compound **5** was also an antagonist but displayed almost no M_1/M_3 receptor subtype selectivity.[8]



1: R^1 = H; X = CH_2; R^2 = H
2: R^1 = H; X = $CHCH_3$; R^2 = H
3: R^1 = H; X = NH; R^2 = H
4: R^1 = H; X = NCHO; R^2 = H
5: R^1 = H; X = $NCOCH_3$; R^2 = H
6: R^1 = CH_3; X = CH_2; R^2 = H
7: R^1 = H; X = CO; R^2 = H
8: R^1 = H; X = CH_2; R^2 = CH_3

The 3-methyl substituted pyrrolidone analogue **6** is the only methyl substituted tertiary amino analogue of **1** which is a full agonist on the guinea pig ileum.[2,6] Muscarinic receptor agonists such as **1** and **6** might be useful in the treatment of the central cholinergic deficiency that has been implicated in patients with Alzheimer's disease (AD).[9] Compound **1** has been tested clinically for treatment of AD but the treatment resulted in severe depressive symptoms, making assessment of its cognitive effects impossible.[10] Development of new muscarinic agonists that

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(2) (a) Dahlbom, R. Structural and Steric Aspects of Compounds Related to Oxotremorine. In *Cholinergic Mechanisms; Phylogenetic Aspects, Central and Peripheral Synapses, and Clinical Significance*; Pepeu, G., Ladinsky, H., Eds.; Plenum: New York, 1981; pp 621–638. (b) Ringdahl, B. Structural Determinants of Muscarinic Agonist Activity. In *The Muscarinic Receptors*; Brown, J. H., Ed.; Humana Press Inc.: Clifton, NJ, 1989; pp 151–218 and references cited therein.
(3) Nilsson, B. M.; Vargas, H. M.; Ringdahl, B.; Hacksell, U. Phenyl Substituted Analogues of Oxotremorine as Muscarinic Antagonists. *J. Med. Chem.* **1992**, *35*, 285–294.
(4) This nomenclature is proposed for the M_2 "glandular/smooth muscle" subtype: Doods, H. N.; Mathy, M.-J.; Davidesko, D.; van Charldorp, K. J.; de Jonge, A.; van Zwieten, P. A. Selectivity of Muscarinic Antagonists in Radioligand and in Vivo Experiments for the Putative M_1, M_2 and M_3 Receptors. *J. Pharmacol. Exp. Ther.* **1987**, *242*, 257–262.
(5) For recent subclassifications of muscarinic receptors based on both pharmacological characterization and molecular cloning studies, see: Levine, R. R.; Birdsall, N. J. M. Subtypes of Muscarinic Receptors IV. Nomenclature for Muscarinic Receptor Subtypes Recommended by Symposium. *Trends Pharmacol. Sci.* **1989**, *10* (Suppl.), VII.
(6) Ringdahl, B.; Jenden, D. J. Stereoselectivity of Oxotremorine Analogues for Muscarinic Receptors in the Isolated Guinea Pig Ileum. *Mol. Pharmacol.* **1983**, *23*, 17–25.
(7) Vargas, H. M.; Ringdahl, B. Centrally Active Antimuscarinic Analogs of Oxotremorine Selectively Block Physostigmine-Induced Hypertension, but Not Peripheral Muscarinic Vasodepression. *J. Pharmacol. Exp. Ther.* **1990**, *253*, 165–170.
(8) Amstutz, R.; Closse, A.; Gmelin, G. Die Position 5 im Oxotremorin-Gerüst: Eine Zentrale Stelle für die Steuerung der Aktivität am Muscarinischen Rezeptor. *Helv. Chim. Acta* **1987**, *70*, 2232–2244.
(9) See, e.g.: DeFeudis, F. V. Central Cholinergic Systems, Cholinergic Drugs and Alzheimer's Disease—An Overview. *Drugs Today* **1988**, *7*, 473–490.
(10) Davis, K. L.; Hollander, E.; Davidson, M.; Davis, B. M.; Mohs, R. C.; Horvath, T. B. Induction of Depression With Oxotremorine in Patients With Alzheimer's Disease. *Am. J. Psychiatry* **1987**, *144*, 468–471.

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Table I. Physical Data of the New Compounds Tested[a]

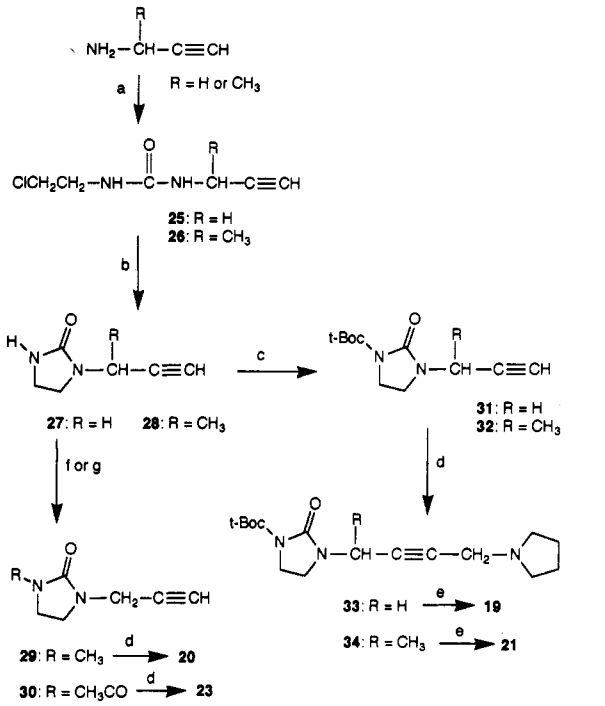
compd	yield	TLC, R_f[b,c]	mp (°C)	formula[d,e]
15	82	0.23 (A)	132–134	$C_{10}H_{17}N_3O\cdot1.5C_2H_2O_4$
16	80	0.33 (A)	114–116	$C_{11}H_{19}N_3O\cdot C_4H_4O_4$
17	83	0.13 (B)	122–124	$C_{11}H_{19}N_3O\cdot HCl$
18	86	0.19 (B)	131–132	$C_{12}H_{21}N_3O\cdot C_2H_2O_4$
19	55[f,g]	0.15 (C)	132–133	$C_{11}H_{17}N_3O\cdot C_2H_2O_4$
20	88	0.42 (C)	121.5–122.5	$C_{12}H_{19}N_3O\cdot C_2H_2O_4$
21	59[h,i]	0.30 (C)	151–152	$C_{12}H_{19}N_3O\cdot C_2H_2O_4$
22	78	0.14 (D)	119–120	$C_{12}H_{17}N_3O_2\cdot C_2H_2O_4$
23	100	0.52 (C)	136.5–138	$C_{13}H_{19}N_3O_2\cdot C_2H_2O_4$
24	65[j]	0.30 (A)	174–176	$C_{11}H_{15}N_3O_2\cdot C_2H_2O_4$

[a] For details of their preparation, see the Experimental Section. [b] R_f values correspond to the free bases. [c] A: alumina [ether–methanol (10%)]. B: silica [chloroform–methanol (10%)]. C: alumina [ether–methanol (5%)]. D: silica (acetone). [d] All compounds were analyzed for C, H, and N. The analytical results obtained were within ±0.4%. [e] The oxalates **15**, **18**, **20–22**, **24**, and **16**·fumarate and **17**·HCl were recrystallized from acetone–methanol–ether. The oxalate salts of **19** and **22** were recrystallized from acetonitrile–methanol–ether and acetonitrile–ether, respectively. [f] Overall yield from **31**. [g] The *N*-*t*-Boc protected precursor **33** was chromatographed on an alumina column using ether as eluent. [h] Overall yield from **32**. [i] The *N*-*t*-Boc protected precursor **34** was chromatographed on a silica column using chloroform–methanol (5%) as eluent. [j] Overall yield from **39**.

are better tolerated and with different profiles (e.g., M_1 receptor selective agonists and/or presynaptic muscarinic antagonists) have been proposed as potentially useful therapeutic agents for the treatment of AD.[11] Among open carboxamide analogues of **1** the partial muscarinic agonist **10** (BM-5)[12] has shown the ability to release acetylcholine in vivo (cortex)[13] and in vitro (hippocampus)[14] by blocking presynaptic muscarinic receptors. Accordingly, it has been proposed that **10** might be a useful lead compound in AD research.[11,15]

In this study a number of modifications of **1** have been made in an attempt to probe possible hydrophilic receptor binding sites at the muscarinic receptors.[16] We have thus prepared and tested pharmacologically a series of N-substituted 2-imidazolidones (**19–23**) and a hydantoin analogue (**24**).[17]

Scheme I[a]



[a] Reagents: (a) 2-chloroethyl isocyanate, Et_3N (cat.), THF or CH_3CN; (b) pulverized KOH, Bu_4NBr (0.2 equiv), THF; (c) di-*tert*-butyl dicarbonate, 4-DMAP, CH_3CN; (d) pyrrolidine, $(HCHO)_n$, CuCl, HOAc, dioxane; (e) CF_3COOH, CH_2Cl_2, 0 → 20 °C; (f) NaH, MeI, THF, 0 → 20 °C; (g) AcCl, Et_3N, ether, 0 → 20 °C.

The *N*-methylacetamido analogue **9** (UH-5)[2b,18] is a muscarinic agonist with pharmacological properties similar to that of **1**. It has 2–3-fold lower affinity to ileal M_3 receptors than **1**, but displays slightly higher efficacy than **1**.[2b,18] Similarly, the propionamide homologues of **9** (i.e., **11**) and **10** (i.e., **12**) retained considerable muscarinic agonist activity on the ileum.[2b] Further methyl substitution at the α-carbon of **9**, giving **13**,[2b] resulted in an antagonist whereas the isosteric *N*,*N*-dimethylurea derivative **14** has been reported[17b,18a] to be a partial muscarinic agonist. Hence, we also prepared the urea analogues **15–18**.

Compounds **15–24** were evaluated for muscarinic and antimuscarinic activity on the guinea pig ileum and for ability to inhibit the binding of the nonselective muscarinic antagonist [^{3}H]-3-quinuclidinyl benzilate ([^{3}H]QNB) to homogenates of the rat cerebral cortex. They were found to be muscarinic agonists, weak partial agonists, or antagonists in the isolated guinea pig ileum.

Chemistry

The synthetic procedures employed are outlined in

(11) Gray, J. L.; Enz, A.; Spiegel, R. Muscarinic Agonists for Senile Dementia: Past Experience and Future Trends. *Trends Pharmacol. Sci.* **1989**, *10* (Suppl.), 85–88.

(12) Resul, B.; Dahlbom, R.; Ringdahl, B.; Jenden, D. J. *N*-Alkyl-*N*-(4-*tert*-amino-1-methyl-2-butynyl)carboxamides, a New Class of Potent Oxotremorine Antagonists. *Eur. J. Med. Chem.-Chim. Ther.* **1982**, *17*, 317–322.

(13) (a) Casamenti, F.; Cosi, C.; Pepeu, G. Effect of BM-5, a Presynaptic Antagonist–Postsynaptic Agonist on Cortical Acetylcholine Release. *Eur. J. Pharmacol.* **1986**, *122*, 288–290. (b) Vargas, H. M.; Chu, T. Effects of BM-5 on Regional Acetycholine Turnover and Muscarinic Receptor Binding in Rat Brain. *Neurosci. Abstr.* **1991**, *17*, 389.

(14) Nordström, Ö.; Alberts, P.; Westlind, A.; Undén, A.; Bartfai, T. Presynaptic Antagonist-Postsynaptic Agonist at Muscarinic Cholinergic Synapses: *N*-Methyl-*N*-(1-methyl-4-pyrrolidino-2-butynyl)acetamide. *Mol. Pharmacol.* **1983**, *24*, 1–5.

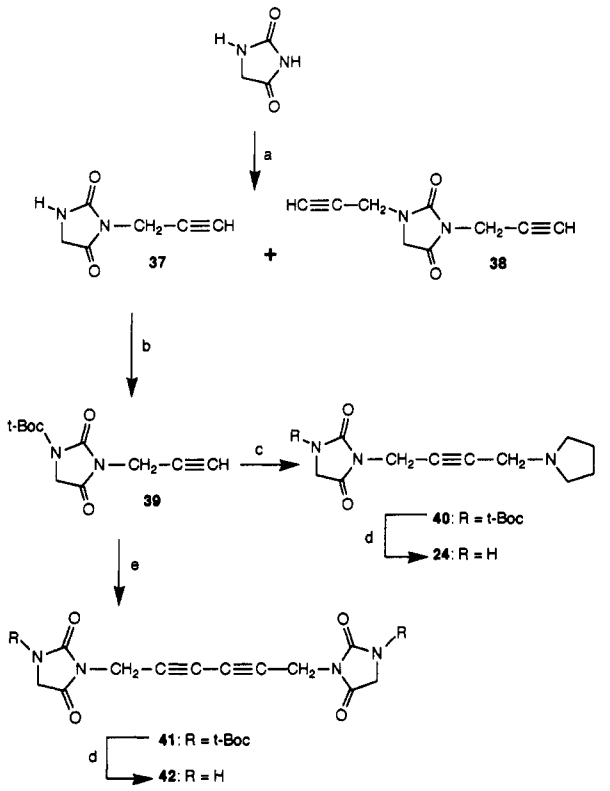
(15) Engström, C.; Undén, A.; Ladinsky, H.; Consolo, S.; Bartfai, T. BM-5, a Centrally Active Partial Muscarinic Agonist with low Tremorogenic Activity. In Vivo and in Vitro Studies. *Psychopharmacology* **1987**, *91*, 161–167.

(16) Recently, a patent has appeared that describes derivatives of **1** substituted with polar substituents in the pyrrolidone ring at the 3 position. Several of these analogues were muscarinic agonists; e.g., the enantiomers of the 3-hydroxy-2-pyrrolidone analogue of **1**. See: Trybulski, E. J.; Kramss, R. H.; Brabander, H. J. United States Patent 4,937,235, 1990. Compare: *Chem. Abstr.* **1990**, *113*, 211824m.

(17) During the preparation of this manuscript, reports have appeared which include the synthesis and the muscarinic activity of **19–21**: (a) Moon, M. W.; Heier, R. F. International Patent N:o WO 90/04588, 1990. Compare: *Chem. Abstr.* **1991**, *114*, 42786p. (b) Moon, M. W.; Chidester, C. G.; Heier, R. F.; Morris, J. K.; Collins, R. J.; Russell, R. R.; Francis, J. W.; Sage, G. P.; Sethy, V. H. Cholinergic Activity of Acetylenic Imidazoles and Related Compounds. *J. Med. Chem.* **1991**, *34*, 2314–2327.

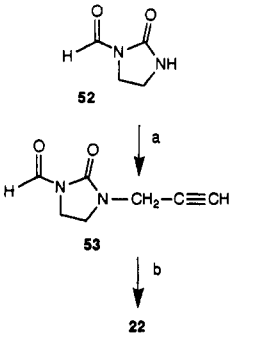
(18) (a) Bebbington, A.; Brimblecombe, R. W.; Shakeshaft, D. The Central and Peripheral Activity of Acetylenic Amines Related to Oxotremorine. *Br. J. Pharmacol.* **1966**, *26*, 56–67. (b) Svensson, U.; Hacksell, U.; Dahlbom, R. Acetylene Compounds of Potential Pharmacological Value. XXV. *N*-(4-Pyrrolidino-2-butynyl)-*N*-alkylcarboxamides. *Acta Pharm. Suec.* **1978**, *15*, 67–70.

Scheme II[a]



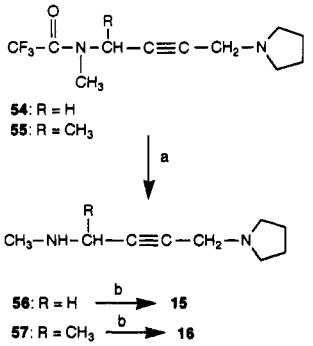
[a] Reagents: (a) propargyl bromide, pulverized KOH, Bu_4NBr (0.1 equiv), THF, 0 °C → reflux; (b) di-*tert*-butyl dicarbonate, 4-DMAP, CH_3CN; (c) pyrrolidine, $(HCHO)_n$, CuCl, HOAc, dioxane; (d) CF_3COOH, CH_2Cl_2, 0 → 20 °C; (e) CuCl (0.3 equiv), Et_3N, dioxane.

Scheme III[a]

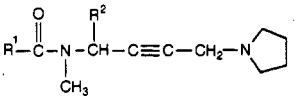


[a] Reagents: (a) NaH, propargyl bromide, THF, 70 °C; (b) pyrrolidine, $(HCHO)_n$, CuCl, HOAc, dioxane.

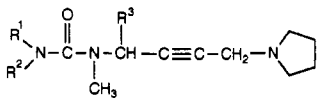
Scheme IV[a]



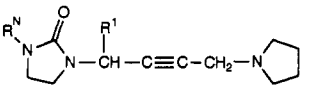
[a] Reagents: (a) 5 M NaOH; (b) KOCN, HOAc, H_2O/THF, 70 °C.



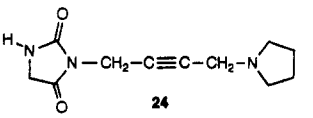
9: $R^1 = CH_3$; $R^2 = H$
10: $R^1 = R^2 = CH_3$
11: $R^1 = CH_3CH_2$; $R^2 = H$
12: $R^1 = CH_3CH_2$; $R^2 = CH_3$
13: $R^1 = (CH_3)_2CH$; $R^2 = H$



14: $R^1 = R^2 = CH_3$; $R^3 = H$
15: $R^1 = R^2 = R^3 = H$
16: $R^1 = R^2 = H$; $R^3 = CH_3$
17: $R^1 = CH_3$; $R^2 = R^3 = H$
18: $R^1 = CH_3$; $R^2 = H$; $R^3 = CH_3$



19: $R^N = R^1 = H$
20: $R^N = CH_3$; $R^1 = H$
21: $R^N = H$; $R^1 = CH_3$
22: $R^N = HCO$; $R^1 = H$
23: $R^N = CH_3CO$; $R^1 = H$



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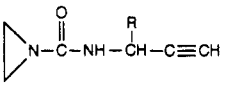
Schemes I–IV. Physical data of the test compounds **15–24** are collected in Table I. The 2-imidazolidones **27**[19] and **28**[20] were prepared in 82 and 72% yield, respectively, by cyclization of the 2-chloroethylureas **25** and **26**, using powdered KOH in the presence of Bu_4NBr in THF (Scheme I). Competitive ring closure occurred during these conditions, since we also isolated *N*-carbamoylaziridine isomers **35** and **36** in 6 and 13% yield, respectively.

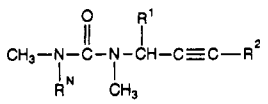


35: R = H
36: R = CH_3

N-Methylation (NaH, iodomethane, THF) or N-acetylation (excess of acetyl chloride and triethylamine)[21] of **27** gave the intermediates **29**[22] and **30** in 99 and 68% yield, respectively. Cuprous-catalyzed Mannich reactions with pyrrolidine afforded test compounds **20** and **23**, respectively (Scheme I).

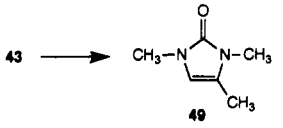
N-Alkylation of 2,4-imidazolidinedione with propargyl bromide and 1,3-dimethylurea with propargyl bromide or 1-methyl-2-propynyl *p*-toluenesulfonate,[23] by use of pow-

(19) This compound was prepared by a similar route without isolation of the urea intermediate **25** in ref 17. However, no formation of byproduct **35** was reported.
(20) Compound **28** was prepared by an alternative route starting from ethylendiamine in ref 17a.
(21) Compare: Nilsson, B. M.; Ringdahl, B.; Hacksell, U. Derivatives of the Muscarinic Agent *N*-Methyl-*N*-(1-methyl-4-pyrrolidino-2-butynyl)acetamide. *J. Med. Chem.* **1988**, *31*, 577–582.
(22) Compound **29** was prepared (in 57% yield) by a similar procedure in ref 17b.



43: $R^N = R^1 = R^2 = H$
44: $R^N = CH_2-C\equiv CH$; $R^1 = R^2 = H$
45: $R^N = H$; $R^1 = CH_3$; $R^2 = H$
46: R^N = t-Boc; $R^1 = R^2 = H$
47: R^N = t-Boc; $R^1 = CH_3$; $R^2 = H$
48: R^N = t-Boc; $R^1 = H$; $R^2 = CH_2NC_4H_8$

dered KOH in the presence of Bu_4NBr in THF, gave the N-alkylated hydantoin **37**[24] (Scheme II) and the urea derivatives **43** and **45** in isolated yields of 52, 20,[25] and 16%, respectively. In addition, the N,N′-dipropargylated hydantoin **38** and the N,N′-dipropargylated urea **44** were obtained in 16 and 8% yield, respectively. The low yields of **43** and **45** appear in part be due to competitive base-catalyzed intramolecular cyclizations of the formed *N*-propargylureas.[26] When **43** was treated with powdered KOH in THF in a separate experiment, we isolated the cyclized product 1,3,5-trimethyl-2-imidazolone (**49**) in 87% yield.[27,28]



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The Mannich reactions of **27**, **28**, and **37** (Schemes I and II), which involve the terminal acetylenic position, are not straightforward since competitive N-aminomethylation

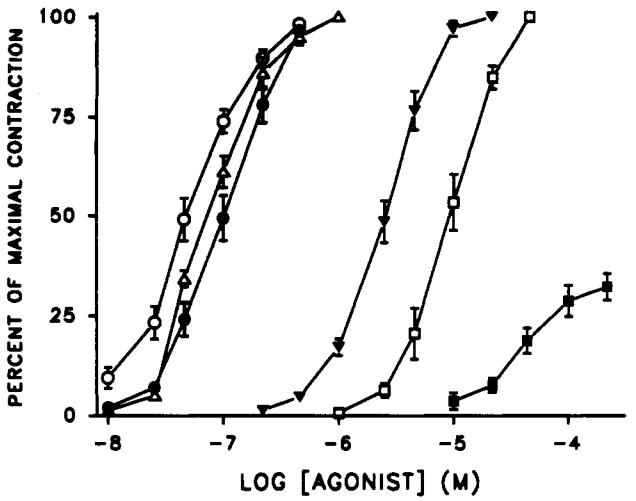


Figure 1. Concentration–response curves of compounds 1 (○), **20** (△), carbachol (●), **17** (▼), **15** (□), and **24** (■) on the isolated guinea pig ileum. Values are means and vertical bars show SE. Number of preparations used are given in Table II.

may occur at the conjugated nitrogens present in these compounds. These latter sites of reaction have previously been reported to participate in Mannich reactions of hydantoins[30] and 2-imidazolidones.[31,32] Therefore, **27**, **28**, and **37** were N-protected as *t*-Boc derivatives. Use of a slight excess of di-*tert*-butyl dicarbonate in the presence of 4-(dimethylamino)pyridine in acetonitrile[33] gave **31** (92%), **32** (96%), and **39** (92%), respectively. In contrast, the *N*-*t*-Boc protections of **43** and **45** were sluggish and the use of more than a 3-fold excess of di-*tert*-butyl dicarbonate and a 10-fold longer reaction time gave only a 47% yield of **46** and a 42% yield of **47**. Subjecting **31**, **32**, **39**, and **46** to the Mannich reaction afforded *N*-*t*-Boc protected Mannich bases **33**, **34**, **40**, and **48** in 85, 59, 81, and 77% yield, respectively (Schemes I and II). However, in contrast to the Mannich reactions performed directly on **27** and **28**, which gave side products (vide supra) and difficulties in the purification step,[34] it was later observed that urea derivatives **43** and **45** underwent the desired Mannich reaction without formation of any detectable side products; **17** and **18** were produced in 83 and 86% yield, respectively. On the other hand, byproducts were isolated from the cuprous-catalyzed Mannich reactions of the *N*-*t*-Boc protected derivatives **32**, **39**, and **46**. These byproducts were identified as the dimeric diynes **50**, **41**, and **51**, respectively, and were probably formed by oxidative coupling[35] of the terminal acetylenic precursors. The

(23) Wunderli, A.; Winkler, T.; Hansen, H.-J. Zur Stereochemie der Aromatischen Claisen-Umlagerung. Thermische Umlagerung von Erythroiden und Threoiden ortho-Dienonen. *Helv. Chim. Acta* **1977**, *60*, 2436–2459.

(24) Compound **37** has previously been prepared in 12% yield: (a) Danielsson, B.; Johansson, S.; Paalzow, L. Some new Substituted Hydantoins. *Acta Pharm. Suec.* **1965** *2*, 155–166. (b) Schulte, K. E.; Reisch, J.; Sommer, M. Intramolekularer Ringschluss bei *N*-Propinyl-barbitursäuren und *N*-Propinylbenzamiden. *Arch. Pharm.* **1966**, *299*, 107–112.

(25) Changing solvent to CH_3CN and/or omitting the phase-transfer catalyst did not influence the yield of **43**. Similarly, running the reaction at −78 → 22 °C did not improve the yield. The yield obtained in these reactions ranged between 13 and 24%.

(26) Such base-catalyzed cyclizations of *N*-propargylic ureas have previously been reported: (a) Reactions of Propargyl Alcohols and Propargylamines with Isocyanates. Shachat, N.; Bagnell, J. J., Jr. *J. Org. Chem.* **1963**, *28*, 991–995. (b) Easton, N. R.; Cassady, D. R.; Dillard, R. D. Reactions of Acetylenic Amines VIII. Cyclization of Acetylenic Ureas. *J. Org. Chem.* **1964**, *29*, 1851–1855.

(27) Compound **43** (0.68 g, 5.4 mmol) was treated with powdered KOH (0.31 g, 5.5 mmol) in THF (10 mL) and the resulting mixture was stirred at room temperature for 18 h. Concentration in vacuo and chromatography of the residue on a silica column with ether followed by ether–methanol (5%) as eluents gave 0.60 g (87%) of **49** as an oil: TLC R_f = 0.30 [SiO_2, ether–methanol (10%)]. ^1H NMR, ^{13}C NMR, and IR spectral data of **49** were in agreement with those reported.[29] Attempts to isolate **49** from the reaction mixture aimed to N-propargylate 1,3-dimethylurea (to give **43**) were unsuccessful due to overlapping spots in the region corresponding to **49** on TLC.

(28) For alternative preparations of **49**, see ref 29 and Harayame, T.; Mori, K.; Yanada, R.; Iio, K.; Fujita, Y.; Yoneda, F. Oxidation of Thymine Derivatives with Superoxide Ion. *J. Chem. Soc., Chem. Commun.* **1988**, 1171–1172.

(29) Cortes, S.; Kohn, H. Selective Reductions of 3-Substituted Hydantoins to 4-Hydroxy-2-imidazolidinones and Vicinal Diamines. *J. Org. Chem.* **1983**, *48*, 2246–2254.

(30) Bombardieri, C. C.; Taurins, A. The Mannich Condensation of Compounds Containing Acidic Imino Groups. *Can. J. Chem.* **1955**, *33*, 923–928.

(31) Trippetta, L.; Orazi, O. O.; Corral, R. A. Sustitucion en el Anillo Hidantoinico y Sistemas Relacionados. Parte IV: Aminometilacion de Acidos Parabanicos y Etilenurea. *An. Asoc. Quim. Argent.* **1965**, *53*, 49–52. Compare: *Chem. Abstr.* **1967**, *66*, 37826n.

(32) See also: Tramontini, M. Advances in the Chemistry of Mannich Bases. *Synthesis* **1973**, 703–775.

(33) Grehn, L.; Gunnarsson, K.; Ragnarsson, U. A Simple Method for tert-Butoxycarbonylation of Amides. *Acta Chem. Scand., Ser. B* **1986**, *40*, 745–750.

(34) However, these byproducts were not reported in ref 17 during the cuprous-catalyzed Mannich reactions of **27** and **28** performed under similar conditions.

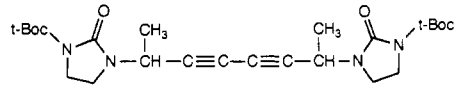
(35) For formation of dialkynes by oxidative coupling of terminal acetylenes, see: Haines, A. H. *Methods for the Oxidation of Organic Compounds*. Academic Press: London, 1985; pp 168–172 and pp 344–346.

Table II. Muscarinic and Antimuscarinic Effects and Receptor Binding Affinities of Some Analogues to Oxotremorine and BM-5[a]

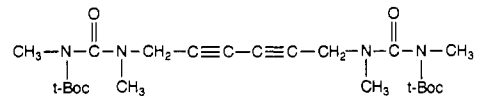
compd	guinea pig ileum					rat cerebral cortex [^{3}H]QNB displacement,
	N[b]	EC_{50},[c,d] μM	K_D[e,f]	E_{max}[g]	efficacy[h]	K_i (μM)[i]
1 (oxotremorine)	6	0.05 ± 0.004	1.2 ± 0.1	1.0	1.0	0.23 ± 0.06
6[j]		0.50 ± 0.03	11.5 ± 2.6	1.0	0.10	
8[k]		0	0.091 ± 0.01	0	0	0.059 ± 0.001
10		0.19 ± 0.03[l]	0.24 ± 0.07[l]	0.83[l]	0.013[l]	0.06
15	4	44.9 ± 7.0	49 ± 7.0	0.57	0.08	10.7 ± 1.0
16	4	0	0.71 ± 0.17[m]	0	0	0.42 ± 0.03
17	4	2.16 ± 0.36	26.4 ± 2.0	1.0	0.53	15.8 ± 1.1
18	5	2.11 ± 0.42	7.5 ± 0.3	1.0	0.18	4.2 ± 0.7
19	4	2.67 ± 0.53	30.3 ± 3.0	1.0	0.49	6.5 ± 0.7
20	5	0.10 ± 0.01	2.9 ± 0.5	1.0	1.21	1.6 ± 0.4
21	4	0	0.48 ± 0.09[m]	0	0	0.64 ± 0.07
22	5	8.6 ± 1.4	20.9 ± 2.0	1.0	0.14	26.4 ± 2.0
23	5	>300		0	0	27.4 ± 0.5
24	4	46.4 ± 0.9	100 ± 8	0.37	0.12	17.2 ± 0.6
carbachol	14	0.12 ± 0.01	18.2 ± 0.8	1.0	5.71	

[a] Values are means plus or minus standard errors. [b] Number of ileal preparations used. [c] The concentration of an agonist or partial agonist that elicits 50% of its own maximum contractile response. [d] The reported EC_{50} values are 1.0, 0.07, 0.42, and 0.42 μM for **7**, **9**, **11**, and **12**, respectively (ref 2b). [e] Dissociation constant of the drug-receptor complex. [f] The reported K_D values are 5.4 and 2.2 μM for **7** and **9**, respectively (ref 2b). [g] The maximum contractile response relative to that elicited by carbachol. [h] Relative efficacies were dermined with oxotremorine as the reference. [i] K_i values were based on three determinations, each performed in triplicate. Hill coefficients were not determined because the competition curves were constructed with only six to seven points. [j] Values are from ref 69. [k] Values are from ref 70. [l] Values are from ref 71. [m] These compounds were competitive antagonists; the Schild slopes were equivalent to 1.

isolated yields were 37%,[36] 7%, and 25%,[37] respectively. Compound **41** was N-deprotected (trifluoroacetic acid in dichloromethane) to confirm the structure of these by-products. The product (**42**; Scheme II) had spectral data (IR, ^{1}H, and ^{13}C NMR[38]) and elemental analysis in accordance with the assigned structure. The N-protecting group was removed by the same procedure from the Mannich bases **33**, **34**, **40**, and **48**, giving test compounds **19**, **21**, **24**, and **17**, respectively.



50



51

N-Formyl derivative **53** was prepared in 78% yield by N-alkylation of **52**[39] with propargyl bromide in the presence of sodium hydride in THF. A Mannich reaction with pyrrolidine furnished test compound **22** (Scheme III). This

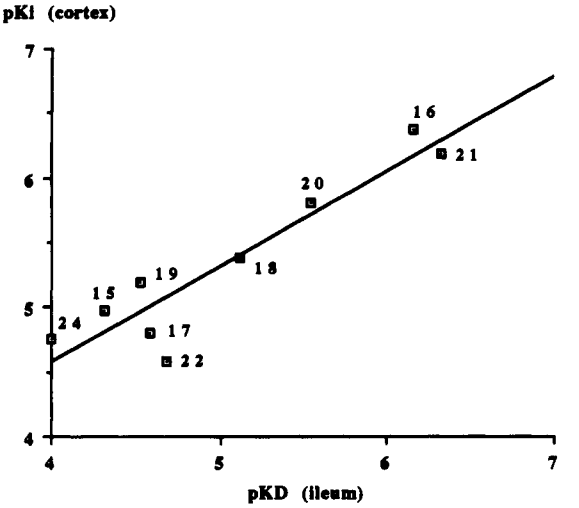


Figure 2. Relationship between dissociation constants (−log K_D) at ileal muscarinic receptors and inhibition of [^{3}H]QNB binding to homogenates of rat cerebral cortex (−log K_i) for the new analogues. Values are from Table II. The regression line is described by pK_i(cortex) = 0.74 × pK_D(ileum) + 1.63 (r^2 = 0.86).

compound proved to be unstable under alkaline conditions (aqueous sodium bicarbonate; pH around 8.5), since it was hydrolyzed in part to **19** (TLC). However, a solution of **22** kept at room temperature over night showed no decomposition at pH 7.4 (phosphate buffer).

The intermediate diamine **57** was prepared (in 88% yield) from the trifluoroacetamide **55**[21] by basic hydrolysis (5 M NaOH) as previously described for the synthesis of **56**[3] from trifluoroacetamide **54**[21] (Scheme IV). The urea derivatives **15** and **16** were prepared in 82 and 80% yield from the corresponding acetylenic diamines **56** and **57**, respectively, by reaction with potassium cyanate[40] in a water–THF mixture containing acetic acid. Compounds **15** and **16** were isolated and tested as the oxalate and the

(36) Byproduct **50** (obtained in addition to **34**) was isolated after column chromatography on a silica column using chloroform–methanol (5%) as eluent. An analytical sample of **50** was obtained after trituration with *n*-hexane: mp 172–174 °C. ^{1}H and ^{13}C NMR spectral data of **50** are given in the supplementary material.

(37) Byproduct **51** (obtained in addition to **48**) was isolated as a viscous oil after chromatography on a silica column using chloroform–methanol (5%) as eluent. ^{1}H and ^{13}C NMR spectral data of **51** are given in the supplementary material.

(38) The assignment of the acetylenic carbons is based on literature data on similar compounds: Huntsman, W. D. Synthetic Acyclic Polyacetylenes. In *The Chemistry of the Carbon–Carbon Triple Bond* (Part 2); Patai, S., Ed.; Wiley (Interscience): Chichester, 1978; pp 553–620.

(39) (a) Corfield, G. C.; Crawshaw, A.; Monks, H. H. *N,N'*-Divinylureas: Further Polymerization Studies and Spectroscopic Investigation of Structure. *J. Macromol. Sci.-Chem.* **1975**, *A9*, 1085–1111. (b) Koenig, H. B.; Schroeck, W.; Metzger, K. G. German Patent 2152967, 1973. Compare: *Chem. Abstr.* **1973**, *79*, 32047t.

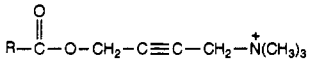
(40) Compare ref 24b and Yura, Y. Studies on Acetylenic Compounds. XXV. Ringclosure. (5). New Synthetic Methods of Heterocyclic Compounds from α-Amino- and α-*N*-substituted Aminoacetylenic Compounds. *Chem. Pharm. Bull.* **1962**, *10*, 1087–1093.

fumarate salts, respectively.[41,42]

Pharmacological Results and Discussion

The muscarinic and antimuscarinic activities in the isolated guinea pig ileum and receptor binding affinities to rat cerebral cortex for **15–24** are shown in Table II. In addition, reference data for **1** and **6–12** are listed in the table. The K_D value represents the equilibrium dissociation constant as determined for the agonists (i.e., Furchgott analysis) or antagonists (i.e., Schild analysis) examined in this study. The derivatives **15**, **17–20**, **22**, and **24** behaved as agonists, though their activities ranged from partial to full agonism (compare Figure 1). Compound **23** was a weak partial agonist and **16** and **21** were devoid of intrinsic activity on the guinea pig ileum and behaved as competitive antagonists. A fairly good correlation ($r^2 = 0.86$) was obtained between affinity for ileal M_3 muscarinic receptors (K_D values) and affinity for cortical muscarinic receptors (K_i values from displacement studies with [^{3}H]QNB) of the novel analogues (Figure 2). Thus, structural requirements for binding to cortical muscarinic receptors closely paralleled those for affinity at ileal M_3 receptors. Similar correlations have been observed among other analogues of **1**.[2b] It should be noted, however, that specific subtype interactions were not examined in this study and the possibility exists that these analogues could express binding preferences for the different muscarinic receptor subtypes.

Replacement of the carbon α to the carbonyl carbon in **1** and in **9** by a nitrogen atom was accompanied by a decrease in muscarinic activity. The 2-imidazolidone analogue **19** was a weak agonist and the urea analogue **15** was a weak partial agonist on the guinea pig ileum. They showed 25- and 22-fold lower affinity for ileal M_3 receptors than their parent compounds, respectively. The decrease in potency was even more pronounced; **19** and **15** were 53- and 640-fold less active than **1** and **9**, respectively, in inducing contractions of the ileum as seen from their EC_{50} values. Similarly, the hydantoin derivative **24**, which may be regarded as a closely related analogue to the succinimide derivative of **1** (i.e., **7**), also displayed low muscarinic activity. Compound **24** was a weak partial muscarinic agonist on the guinea pig ileum and displayed 19-, 46-, and 2-fold reductions in affinity, potency, and relative efficacy, respectively, as compared to **7** which has been reported to be a full agonist in this preparation.[2b] Similar to these structural modifications is the previously described replacement of the acetyl methyl group in the acetylenic ester **58** by a amino group giving **59**. The carbamate **59** was 15-fold less potent in inducing contractions of the rabbit jejunum than the ester analogue **58**.[43]



58: R = CH_3
59: R = NH_2

The C1-methyl substituted derivatives **16** and **21** were competitive antagonists in the ileal assay (i.e., the slopes of their Schild plots were equivalent with unity). They exhibited 69- and 63-fold higher affinity for ileal muscarinic receptors than their C1-desmethyl analogues **15** and **19**, respectively. The urea analogue **16**, which is structurally related to the partial agonist **10**, showed only 3-fold lower affinity than the latter compound for ileal M_3 receptors. Similarly, **21** showed 5-fold lower affinity for the same receptors than the C1-methyl substituted 2-pyrrolidone **8**.[44]

It has been observed previously[2b] that the intrinsic muscarinic activity at ileal M_3 receptors is preserved when a methyl group is introduced α to the carbonyl carbon in **1**, **9**, and **10**, giving **6**, **11**, and **12**. However, the potency is lowered 10-, 6-, and 2-fold, respectively (EC_{50} values). Analogous methyl substitution at the N-3 position in the 2-imidazolidone **19**, giving **20**, resulted in the most potent muscarinic agonist of the new analogues; a 2.5-fold increase in efficacy, a 26-fold increase in potency, and a 10-fold increase in affinity relative to that of **19** was observed. When compared to the corresponding 3-methyl-2-pyrrolidone analogue **6**,[6] compound **20** showed 5-, 4-, and 12-fold elevations in potency, affinity, and relative efficacy in the guinea pig ileum.

Introduction of a single methyl group in the N-3 position of the acyclic analogues **15** and **16**, to give **17** and **18**, changed the muscarinic profile from partial agonism and antagonism, respectively, to full agonism in the guinea pig ileum.[44] However, a 5-fold decrease in muscarinic potency (EC_{50} values) was observed for the *N*-3-methyl substituted urea derivatives **17** and **18** as compared to their propionamide analogues **11** and **12**,[2b] respectively.

The *N*-formyl substituted imidazolidone analogue **22** was a full agonist in the guinea pig ileum with slightly higher (1.5-fold) affinity than the N-3 unsubstituted imidazolidone analogue **19**. The corresponding *N*-acetyl analogue of **19** (i.e. **23**) showed poor stimulant activity of ileum (>300 μM produced 20–30% of maximal contraction relative to that of carbachol) and was not further studied. A decreased electron density at the imidazolidone carbonyl group might explain the observed reduction in muscarinic activity of *N*-formyl compound **22** when compared to **20**. In the IR spectra of the free bases the imidazolidone C=O stretching frequency appear at 1725 and 1700 cm^{-1} for **22** and **20**, respectively.[45] The substantial reduction in muscarinic activity of **23** as compared to **22** suggests that the steric bulk of the acetyl methyl group interferes negatively with the drug–receptor interaction. On the basis of the set of acetylenic analogues studied, the replacement of the 2-pyrrolidone or the acetamide moiety in the parent compounds with a more polar 2-imidazolidone or urea moiety appears to result in an attenuation of muscarinic activity (i.e., ileal muscarinic receptor affinity and efficacy). On the other hand, introduction of a methyl group in the N-3 position of **19**, giving **20**, increased muscarinic agonist activity. The unexpectedly low muscarinic activity of **15**, **19**, and **24** might be due to the ability of the NH and the NH_2 groups, which form part of the urea functions, to donate hydrogen bonds to water. Most likely, these compounds exhibit an increased hydrophilicity as compared to the parent compounds **9**, **1**, and **7**, respectively.[46] This

(41) It might be more convenient to store the crystalline base forms of **15** and **16**, which are water soluble, since the oxalate of **15** and the fumarate salt of **16** turned yellowish upon storage at room temperature for 1.5–2 years.

(42) ^{1}H and ^{13}C NMR spectral data of the oxalate salt of **15** and the fumarate salt of **16** are presented in the supplementary material. For the base forms, see the Experimental Section.

(43) Roszkowski, A. P.; Yelnosky, J. Structure–Activity Relationships Among a Series of Acetylenic Carbamates Related to McN-A-343. *J. Pharmacol. Exp. Ther.* **1967**, *156*, 238–245.

(44) It should be noted that **16**, **18**, and **21** are racemic mixtures. This might have implications on the interpretation of the pharmacological results.

(45) For a similar discussion attempting to explain differences in muscarinic activity among other oxotremorine analogues, see ref 18a.

(46) Compare: Spivak, C. E.; Yadav, J. S.; Shang, W.-C.; Hermsmeier, M.; Gund, T. Carbamyl Analogues of Potent Nicotinic Agonists: Pharmacology and Computer-Assisted Molecular Modeling Study. *J. Med. Chem.* **1989**, *32*, 305–309.

might result in an unfavorable partition between the aqueous phase and the receptor phase and would thereby increase the energy for desolvation which precedes the ultimate binding to the receptor.[46,47] The increased muscarinic potency of the N-3 methyl substituted urea derivative 17 as compared to the N-3 unsubstituted analogue 15 might in part be due to a decreased energy barrier for desolvation, since 17 should be less hydrophilic than 15 and only is able to donate one hydrogen bond.

Experimental Section

Chemistry. General Comments. Melting points (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus. IR spectra were recorded on a Perkin-Elmer 298 infrared spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL FX 90Q spectrometer at 89.55 and 22.5 MHz, respectively, unless otherwise noted, and were referenced to internal tetramethylsilane. Dioxane (3.6 and 68.0 ppm, respectively) was used as internal reference for the ^1H and ^{13}C NMR spectra of the oxalate salts of 18 and 24. Assignments of ^{13}C NMR resonances are frequently based on off-resonance spectra. All spectra were in accordance with the assigned structures. Reactions were carried out under N_2. Thin-layer chromatography was carried out on aluminum sheets precoated with silica gel 60 F_{254} (0.2 mm) or aluminum oxide 60 F_{254} neutral (type E, E. Merck). Column chromatography was performed on silica using Kieselgel 60 (230–400 mesh, E. Merck) or on alumina using Aluminum oxide 90 (E. Merck). Chromatographic spots were visualized by aqueous $KMnO_4$ spraying (or UV detection; 49). The elemental analyses were performed by Mikro Kemi AB, Uppsala, Sweden, or Analytische Laboratorien, Gummersbach, Germany, and were within ±0.4% of the calculated values unless otherwise noted.

1-(2-Chloroethyl)-3-(1-methyl-2-propynyl)urea (26). 2-Chloroethyl isocyanate (1.24 g, 11.7 mmol) was added by use of a syringe and during 5 min to a stirred mixture of 1-methyl-2-propynylamine hydrochloride[49] (1.15 g, 10.9 mmol) and triethylamine (1.34 g, 13.3 mmol) in acetonitrile (50 mL). The mixture was stirred at room temperature for 6 h. Concentration in vacuo gave a solid residue which was dissolved in a small volume of dichloromethane–methanol (2.5%). Column chromatography on silica using gradient elution with *n*-hexane, *n*-hexane–ether (1:1), and ether gave 1.63 g (86%) of 26 as a white solid: mp 82–84 °C; TLC R_f = 0.55 (SiO_2, ether); IR (KBr disk) 3320, 3280, 1620, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.91–5.51 (m, 2 NH), 4.81–4.37 (m, C1-H), 3.79–3.41 (m, CH_2CH_2), 2.28 (d, J = 2.4 Hz, C3-H), 1.42 (d, J = 7.0 Hz, C1-CH_3); ^{13}C NMR (CD_3OD) δ 159.42 (C=O), 85.89 (C2), 71.03 (C3), 44.84 and 42.90 (CH_2's), 38.39 (C1), 22.95 (C1-CH_3). Anal. ($C_7H_{11}ClN_2O$) C, H, N.

1-(2-Chloroethyl)-3-(2-propynyl)urea (25). Compound 25 was prepared by the above method from propargylamine (1.59 g, 29 mmol), 2-chloroethyl isocyanate (2.91 g, 28 mmol), and triethylamine (0.18 g, 1.8 mmol), in THF (50 mL). The yield of 25 after column chromatography was 4.21 g (95%). An analytical sample was obtained after trituration with *n*-hexane: mp 90.5–92.5 °C; TLC R_f = 0.42 (SiO_2, ether); IR (KBr disk) 3330, 3285, 1620 (br) cm^{-1}; ^1H NMR (CD_3OD) δ 3.89 (d, J = 2.4 Hz, C1-H's), 3.68–3.33 (m, CH_2CH_2), 2.54 (t, J = 2.4 Hz, C3-H); ^{13}C NMR (CD_3OD) δ 160.01 (C=O), 81.69 (C2), 71.71 (C3), 44.75 and 42.93 ($ClCH_2CH_2N$), 30.14 (C1). Anal. ($C_6H_9ClN_2O$) C, H, N.

***N*-(1-Methyl-2-propynyl)-2-imidazolidone (28).**[20] Bu_4NBr (0.85 g, 2.63 mmol) and powdered KOH (0.92 g, 16.5 mmol) were added to a stirred solution of 26 (2.30 g, 13.2 mmol) in THF (65 mL). The resulting mixture was stirred at room temperature for 4.5 h. Concentration in vacuo and column chromatography of the oily residue on silica using gradient elution with *n*-hexane–ether, ether, and ether–methanol (5%) gave 1.28 g (70%) of 28. An analytical sample was obtained after trituration of the solid product with *n*-hexane: mp 86.5–88 °C (lit.[17a] mp 90–92 °C); TLC R_f = 0.43 [SiO_2, ether–methanol (5%)]; IR[50] (KBr disk) 3260, 3235, 2105, 1695 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.92 (br, NH), 4.83 (qd, J = 7.2 and 2.4 Hz, C1-H), 3.71–3.32 (m, ring CH_2's), 2.29 (d, J = 2.2 Hz, C3-H), 1.38 (d, J = 7.2 Hz, C1-CH_3); ^{13}C NMR[51] ($CDCl_3$) δ 162.05 (C=O), 81.97 (C2), 71.50 (C3), 40.31 (ring CH_2'), 39.69 (C1), 37.96 (ring CH_2''), 19.53 (C1-CH_3). Anal. ($C_7H_{10}N_2O$) C, H, N.

In addition, 0.23 g (13%) of *N*-[*N*-(1-methyl-2-propynyl)carbamoyl]aziridine (36) was obtained as an oil which solidified in the freezer: mp 44–46 °C; TLC R_f = 0.60 [SiO_2, ether–methanol (5%)]; IR (KBr disk) 3240, 2115, 1685 (br), 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.40 (br, NH), 4.71–4.37 (m, C1-H), 2.24 (d, J = 2.2 Hz, C3-H), 2.09 (s, ring CH_2's), 1.34 (d, J = 7.0 Hz, C1-CH_3); ^{13}C NMR ($CDCl_3$) δ 164.03 (C=O), 84.01 (C2), 70.24 (C3), 37.96 (C1), 26.14 (ring CH_2's), 22.06 (C1-CH_3). Anal. ($C_7H_{10}N_2O$) C, H, N.

***N*-(2-Propynyl)-2-imidazolidone (27).**[17b] This compound was prepared from 25 as described for 28. The reaction was started at 0 °C (ice bath). The temperature was then allowed to reach room temperature. The yield after column chromatography was 82%. An analytical sample was obtained after recrystallization from acetone–ether–*n*-hexane: mp 119–121 °C (lit.[17b] mp 123–125 °C); TLC R_f = 0.33 [SiO_2, ether–methanol (5%)]; IR (KBr disk) 3260, 3220 (shoulder), 2110, 1680 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.68 (br, NH), 4.01 (d, J = 2.6 Hz, C1-H's), 3.62–3.35 (m, ring CH_2's), 2.25 (t, J = 2.6 Hz, C3-H); ^{13}C NMR ($CDCl_3$) δ 162.42 (C=O), 78.02 (C2), 72.12 (C3), 44.30 and 37.90 (ring CH_2's), 33.24 (C1). Anal. ($C_6H_8N_2O$) C, H, N.

The byproduct *N*-[*N*-(2-propynyl)carbamoyl]aziridine (35) was isolated from another batch of 27 as an oil in 6% yield: ^1H NMR ($CDCl_3$) δ 6.12 (br, NH), 3.97 (dd, J = 5.5 and 2.4 Hz, C1-H's), 2.23 (t, J = 2.6 Hz, C3-H), 2.13 (s, ring CH_2's); ^{13}C NMR ($CDCl_3$) δ 164.74 (C=O), 79.53 (C2), 71.13 (C3), 30.03 (C1), 25.95 (ring CH_2's).

1-Methyl-3-(2-propynyl)-2-imidazolidone (29).[17b,52] A solution of 27 (0.77 g, 6.20 mmol) in THF (10 mL) was added to a stirred mixture of sodium hydride (0.22 g of a 80% dispersion in mineral oil, 7.3 mmol, freed from mineral oil by *n*-hexane washings) in THF (15 mL) at 0 °C (ice bath). Iodomethane (2.27 g, 16.0 mmol) was added after 15 min and the mixture was stirred for 2 h while the temperature was allowed to reach room temperature. Concentration in vacuo and column chromatography of the residue on silica using dichloromethane–methanol (2.5%) as eluent afforded 0.85 g (99%) of 29 as an oil. An analytical sample was obtained after distillation: bp 97–98 °C (0.5–0.7 mmHg). Upon storage in the freezer 29 solidified: mp 34.5–36 °C (lit.[17b] mp 57–59 °C); TLC R_f = 0.30 (SiO_2, ether); IR (KBr disk) 3220, 2100, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.00 (d, J = 2.6 Hz, C1-H's), 3.43–3.31 (m, ring CH_2's), 2.80 (s, CH_3), 2.28 (t, J = 2.4 Hz, C3-H); ^{13}C NMR ($CDCl_3$) δ 160.48 (C=O), 77.99 (C2), 72.00 (C3), 44.51 and 41.64 (ring CH_2's), 33.79 (C1), 30.89 (CH_3). Anal. ($C_7H_{10}N_2O$) C, H, N.

1-Acetyl-3-(2-propynyl)-2-imidazolidone (30). Acetyl chloride (6.26 g, 80 mmol) was added dropwise to a stirred mixture of 27 (0.9 g, 7.97 mmol) and triethylamine (4.03 g, 40 mmol) in ether (100 mL) at 0 °C (ice bath). The temperature was allowed to rise to room temperature and the mixture was stirred for 2.5 h. The reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution (300 mL) and stirred for 1 h at room temperature. Extraction with ether (6 × 125 mL), drying ($MgSO_4$) of the combined ether layers, filtration, and concentration in vacuo

(47) However, as noted by one of the referees, similar substitutions in acetylcholine (i.e., giving carbachol) and in azabicycloalkyloxadiazole[48] analogues led to potent muscarinic agonists.

(48) Saunders, J.; Cassidy, M.; Freedman, S. B.; Harley, E. A.; Iversen, L. L.; Kneen, C.; MacLeod, A. M.; Merchant, K. J.; Snow, R. J.; Baker, R. Novel Quinuclidine Based Ligands for the Muscarinic Cholinergic Receptor. *J. Med. Chem.* **1990**, *33*, 1128–1138.

(49) Marszak-Fleury, A. Contribution a l'étude des Amines Primaires Acétyléniques. *Ann. Chim. (Paris)* **1958**, *13*, 656–711.

(50) For IR spectral data of substituted 2-imidazolidones, see: ref 39a and Kohn, H.; Cravey, M. J.; Arceneaux, J. H.; Cravey, R. L.; Willcott, M. R. Syntheses and Spectral Properties of Substituted Imidazolidones and Imidazolines. *J. Org. Chem.* **1977**, *42*, 941–948.

(51) For ^{13}C NMR spectral data of 2-imidazolidones, see: Flaster, H.; Kohn, H. Syntheses and Spectral Properties of 2-Thiobiotin and Biotin Derivatives. *J. Heterocycl. Chem.* **1981**, *18*, 1425–1436.

(52) For an alternative preparation of 29, see ref 17a.

gave the crude product. This material was chromatographed on a silica column using ether–*n*-hexane (1:1) followed by ether as eluents to afford 0.90 g (68%) of **30** as a solid. An analytical sample was obtained after recrystallization from ether–*n*-hexane: mp 92–93 °C; TLC R_f = 0.46 (SiO_2, ether); IR (KBr disk) 3200, 2100, 1725 (ring C=O),[53] 1670 (CH_3C=O)[53] cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.11 (d, J = 2.4 Hz, C1-H's), 3.99–3.42 (m, ring CH_2's), 2.49 (s, CH_3), 2.37 (t, J = 2.6 Hz, C3-H); ^{13}C NMR ($CDCl_3$) δ 170.27 (CH_3CO), 154.09 (NCON), 76.69 (C2), 72.92 (C3), 39.82 and 39.14 (ring CH_2's), 33.02 (C1), 23.02 (CH_3). Anal. ($C_8H_{10}N_2O$) C, H, N.

3-(2-Propynyl)-2,4-imidazolidinedione (37).[24] Bu_4NBr (0.80 g, 2.48 mmol) and powdered KOH (1.12 g, 20.0 mmol) were added to a stirred suspension of 2,4-imidazolidinedione (2.0 g, 20.0 mmol) in THF (15 mL) at 0 °C (ice bath). Propargyl bromide (2.38 g, 20.0 mmol) was added to the resulting mixture and the ice bath was removed after 15 min. Stirring was continued for 24 h at room temperature and then under reflux for 6 h. The precipitate formed was filtered off and the filtercake was washed with dichloromethane. The filtrate was concentrated in vacuo and the semisolid residue was purified by column chromatography. Elution with ether gave 0.28 g (16%) of the N,N'-dialkylated byproduct 1,3-dipropargyl-2,4-imidazolidinedione (**38**) as a solid. An analytical sample of **38** was obtained after recrystallization from acetone–ether–*n*-hexane: mp 80–81.5 °C; TLC R_f = 0.68 (SiO_2, ether); IR (KBr, disk) 3225, 2120, 1770, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.28 and 4.26 (overlapping d's, J's = 2.4 Hz, 2 CH_2C≡CH), 4.03 (s, ring CH_2), 2.41 and 2.28 (t's, J's = 2.4 Hz, 2 C≡CH); ^{13}C NMR ($CDCl_3$) δ 168.20 (CH_2C=O), 154.70 (NCON), 76.54 and 76.26 (2 C≡CH), 73.82 and 71.63 (2 C≡CH), 48.77 (ring CH_2), 32.16 and 27.90 (2 CH_2C≡CH). Anal. ($C_9H_8N_2O_2$) C, H, N. Further elution with ether–methanol (3%) gave 1.6 g (57%) of **37** as a solid: mp 114–117 °C (lit. mp 119–121 °C,[24a] 186–187 °C[24b]); TLC R_f = 0.47 [SiO_2, ether–methanol (5%)]; IR[54] (KBr disk) 3260, 3200 (br), 2120, 1770, 1715 (br) cm^{-1}; ^1H NMR (CD_3OD) δ 4.23 (d, J = 2.6 Hz, C1-H's), 3.98 (s, ring CH_2), 2.62 (t, J = 2.4 Hz, C3-H); ^{13}C NMR[55] (CD_3OD) δ 172.89 (CH_2C=O), 158.71 (NCON), 78.29 (C2), 72.45 (C3), 47.40 (ring CH_2), 28.13 (C1). Anal. ($C_6H_6N_2O_2$) C, H, N.

1,3-Dimethyl-1-(2-propynyl)urea (43). Compound **43** was prepared by a similar procedure as described for **37** from 1,3-dimethylurea (3.31 g, 37.6 mmol), powdered KOH (1.58 g, 28.2 mmol), Bu_4NBr (1.2 g, 3.72 mmol), and propargyl bromide (4.47 g, 37.6 mmol). The reaction mixture was stirred for 3 h at room temperature and worked up as described for **37**. This gave 0.72 g (20%) of **43** obtained as a white solid. An analytical sample was obtained after recrystallization from ether–*n*-hexane: mp 70–71.5 °C; TLC R_f = 0.44 [SiO_2, ether–methanol (5%)]; IR (KBr disk) 3385, 3250, 2110, 1630, 1545 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.85 (br, NH), 4.12 (d, J = 2.4 Hz, C1-H's), 2.94 (s, $CONCH_3$), 2.81 (d, J = 4.6 Hz, CH_3NH), 2.24 (t, J = 2.6 Hz, C3-H); ^{13}C NMR ($CDCl_3$) δ 158.84 (C=O), 79.53 (C2), 71.84 (C3), 37.83 (C1), 33.69 ($CONCH_3$), 27.67 (CH_3NH). Anal. ($C_6H_{10}N_2O$) C, H, N.

In addition, 0.18 g (8%) of 1,3-dimethyl-1,3-dipropargylurea (**44**) was obtained as an oil which solidified when stored in the freezer. An analytical sample was obtained after recrystallization from *n*-hexane–ether: mp 47.5–49.5 °C; TLC R_f = 0.70 (SiO_2, ether); IR (KBr disk) 3220, 2100, 1630, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.94 (d, J = 2.4 Hz, 2 CH_2), 2.92 (s, 2 CH_3), 2.26 (t, J = 2.4 Hz, 2 C≡CH); ^{13}C NMR ($CDCl_3$) δ 163.65 (C=O), 79.37 (2 C≡CH), 72.24 (2 C≡CH), 40.03 (2 CH_2), 36.16 (2 CH_3). Anal. ($C_9H_{12}N_2O$) C, H, N.

1,3-Dimethyl-1-(1-methyl-2-propynyl)urea (45). A mixture of 1,3-dimethylurea (3.97 g, 45.1 mmol), Bu_4NBr (2.1 g, 6.51 mmol), powdered KOH (2.05 g, 36.5 mmol), and THF (80 mL) was stirred at 0 °C (ice bath). 1-Methyl-2-propynyl *p*-toluenesulfonate[23] (7.98 g, 35.6 mmol) was added to the mixture after 2 h. The reaction temperature was allowed to reach room temperature, and the mixture was stirred for a further 20 h and was finally heated to 60 °C for 4 h. The reaction mixture was worked up as described for **37**. After purification by column chromatography, the product was triturated with *n*-hexane. This afforded 0.80 g (16%) of pure **45** as a white solid: mp 84.5–85.5 °C; TLC R_f = 0.47 [SiO_2, ether–methanol (5%)]; IR (KBr disk) 3375, 3220, 2100, 1620, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.35 (qd, J = 7.1 and 2.4 Hz, C1-H), 4.95 (br, NH), 2.86 (s, $CONCH_3$), 2.80 (d, J = 4.6 Hz, CH_3NH), 2.29 (d, J = 2.4 Hz, C3-H), 1.32 (d, C1-CH_3); ^{13}C NMR ($CDCl_3$) δ 158.04 (C=O), 83.30 (C2), 71.13 (C3), 42.07 (C1), 28.58 (CON-CH_3), 27.46 (CH_3NH), 19.74 (C1-CH_3). Anal. ($C_7H_{12}N_2O$) C, H, N.

General Procedure for *t*-Boc Acylation of 27, 28, 37, 43, and 45. Preparation of 1-(*tert*-Butyloxycarbonyl)-3-(2-propynyl)-2,4-imidazolidinedione (39). A solution of di-*tert*-butyl dicarbonate[56] (1.74 g, 7.99 mmol) in acetonitrile (3 mL) was added to a stirred mixture of **37** (0.96 g, 6.95 mmol) and 4-(dimethylamino)pyridine (0.13 g, 1.04 mmol) in acetonitrile (9 mL). The mixture was stirred at room temperature for 3 h. The viscous oily residue obtained after evaporation of the solvent was dissolved in a small volume of dichloromethane and chromatographed on a silica column using ether–light petroleum (1:1) as eluent. This gave 1.5 g (92%) of **39** as a colorless oil: TLC R_f = 0.27 [SiO_2, ether–light petroleum (1:1)]; IR (neat liquid) 3265, 2120, 1820, 1805 (shoulder), 1740 (br) cm^{-1}; ^1H NMR (CD_3OD) δ 4.30 (s, ring CH_2), 4.26 (d, J = 2.6 Hz, C1-H's), 2.65 (t, J = 2.6 Hz, C3-H), 1.54 [s, $C(CH_3)_3$]; ^{13}C NMR (CD_3OD)[57] δ 168.53 (CH_2C=O), 152.94 and 149.57 (C=O's), 84.93 (C—O), 77.58 (C2), 73.01 (C3), 49.97 (ring CH_2), 28.57 (C1), 28.17 [$C(CH_3)_3$]. Anal. ($C_{11}H_{14}N_2O_4$) C, H, N.

1-(*tert*-Butoxycarbonyl)-3-(2-propynyl)-2-imidazolidone (31). The title compound was prepared by the above procedure from **27** and was obtained as a white solid in 92% yield: mp 65–67 °C; TLC R_f = 0.54 (SiO_2, ether); IR (KBr disk) 3265, 2115, 1770, 1690 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.08 (d, J = 2.6 Hz, C1-H's), 3.93–3.70 and 3.58–3.33 (m's, ring CH_2's), 2.25 (t, J = 2.4 Hz, C3-H), 1.53 [s, $C(CH_3)_3$]; ^{13}C NMR ($CDCl_3$) δ 153.44 and 150.32 (C=O's), 82.06 (C—O), 77.00 (C2), 72.68 (C3), 40.31 and 39.91 (ring CH_2's), 32.99 (C1), 27.80 [$C(CH_3)_3$]. Anal. ($C_{11}H_{16}N_2O_3$) C, H, N.

1-(*tert*-Butoxycarbonyl)-3-(1-methyl-2-propynyl)-2-imidazolidone (32). Compound **32** was prepared similarly from **28** and was obtained as a viscous oil in 96% yield which crystallized from *n*-hexane: mp 57.5–59.5 °C; TLC R_f = 0.71 (SiO_2, ether); IR (KBr disk) 3250, 2110, 1725, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.95 (qd, J = 7.1 and 2.2 Hz), 3.94–3.21 (m, ring CH_2's), 2.32 (d, J = 2.4 Hz, C3-H), 1.53 [s, $C(CH_3)_3$], 1.39 (d, J = 7.2 Hz, C1-CH_3); ^{13}C NMR ($CDCl_3$) δ 152.88 and 150.35 (C=O's), 81.91 (C—O), 81.05 (C2), 72.06 (C3), 40.31 (ring CH_2'), 39.66 (C1), 36.26 (ring CH_2''), 27.77 [$C(CH_3)_3$], 19.12 (C1-CH_3). Anal. ($C_{12}H_{18}N_2O_3$) C, H, N.

1-Formyl-2-imidazolidone (52). This compound was prepared according to a literature procedure[39] in 72% yield: mp 155–157 °C (lit. mp 151–152 °C,[39a] 156–158 °C,[39b]); ^1H NMR (CD_3OD) δ 8.82 (s, HC=O), 3.96–3.41 (m's, CH_2's); ^{13}C NMR (CD_3OD) δ 161.79 (HC=O), 158.60 (NCON), 40.27 and 38.62 (CH_2's).

1-Formyl-3-(2-propynyl)-2-imidazolidone (53). Compound **52** (1.35 g, 11.9 mmol) was added to a stirred mixture of sodium hydride (0.38 g of a 80% dispersion in mineral oil, 12.5 mmol, freed from mineral oil by *n*-hexane washings) in THF (35 mL). Propargyl bromide (2.12 g, 17.8 mmol) was added to the mixture, which was heated to 70 °C (oil-bath temperature) for 9.5 h. The precipitate formed was filtered off and the resulting filter cake was washed with dichloromethane. The filtrate was concentrated in vacuo, and the crude oily residue was chromatographed on a silica column using ether–light petroleum followed by ether as eluents. This gave 1.42 g (78%) of **53** as a pale yellow oil: TLC R_f = 0.36 (SiO_2, ether); IR (neat liquid) 3255, 2120, 1735 (ring C=O),[58] 1690 (HC=O)[58] cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.91 (s,

(53) These assignments were based on literature data given in ref 50.

(54) For IR spectral data of substituted hydantoins, see refs 24a and 29.

(55) For ^{13}C NMR spectral data of substituted hydantoins, see ref 29 and Fujiwara, H.; Bose, A. K.; Manhas, M. S.; van der Veen, J. M. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1573–1577.

(56) 3.3 equiv of reagent was used in the N protection of **43** and **45**, respectively.

(57) In the ^{13}C NMR spectrum taken in $CDCl_3$, the signal due to C1 and the signal due to the methyl groups in the *t*-Boc group are overlapping.

HC=O), 4.15 (d, J = 2.7 Hz, C1-H's), 3.96–3.52 (ring CH_2's), 2.43 (t, J = 2.4 Hz, C3-H); ^{13}C NMR ($CDCl_3$) δ 159.74 (HC=O), 154.02 (NCON), 76.29 (C2), 73.26 (C3), 40.87 and 36.67 (ring CH_2's), 32.47 (C1). Anal. ($C_7H_8N_2O_2$) H, N; C: calcd, 55.26; found, 54.78.

***N*,1-Dimethyl-4-(1-pyrrolidinyl)-2-butynylamine (57).** A mixture of trifluoroacetamide derivative **55**[21] (1.76 g, 6.69 mmol) and 5 M aqueous NaOH (35 mL) was stirred at room temperature for 15 h. Extraction with ether (4 × 125 mL), drying (K_2CO_3), filtration, and concentration of the ether layers in vacuo gave crude **57**. This material was chromatographed on an alumina column using ether followed by ether–methanol (5%) as eluents. This gave 0.99 g (88%) of **57** as a colorless oil. The fumarate salt was prepared and recrystallized from acetone–methanol–ether; mp 127–129.5 °C; TLC R_f = 0.57 [free base on alumina, ether–methanol (10%)]; IR (free base, neat liquid) 3260 cm^{-1}; ^1H NMR (fumarate, CD_3OD) δ 6.65 (s, CH=CH), 4.04 (d, J = 1.8 Hz, C4-H's), 3.40–3.11 (m, obscured in part by solvent peaks, pyrrolidine α-H's), 2.74 (s, CH_3NH), 2.15–1.91 (m, pyrrolidine β-H's), 1.57 (d, J = 6.8 Hz, C1-CH_3); ^{13}C NMR (fumarate, CD_3OD) δ 172.64 (C=O's), 136.54 (CH=CH), 83.94 and 79.62 (acetylenic C's), 53.98 (pyrrolidine α-C's), 47.44 (C1), 43.61 (C4), 31.10 (CH_3NH), 24.46 (pyrrolidine β-C's), 18.62 (C1-CH_3). Anal. ($C_{10}H_{18}N_2 \cdot 1.5C_4H_4O_4$) C, H, N.

1-Methyl-1-[4-(1-pyrrolidinyl)-1-methyl-2-butynyl]urea (16). A solution of potassium cyanate (0.73 g, 8.95 mmol) in water (15 mL) was added to a stirred solution of **57** (0.97 g, 5.80 mmol), glacial acetic acid (0.52 g, 8.71 mmol) and THF (15 mL). The resulting mixture was heated to 70 °C (oil-bath temperature) for 5 h. The progress of the reaction was followed by TLC analyses on silica using a mixture of chloroform–methanol (10%) and a few drops of concentrated aqueous NH_4OH as the eluent. The reaction mixture was alkalinized by addition of 10% aqueous K_2CO_3 solution (50 mL) under external cooling (ice bath) and was extracted with dichloromethane (4 × 125 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated in vacuo. The light brown oily residue obtained was chromatographed on an alumina column using gradient elution with ether–methanol (5→10%). This gave 0.98 g (80%) of **16** as a solid. An analytical sample was obtained after recrystallization from ether–*n*-hexane: mp 80–81.5 °C; TLC R_f = 0.33 [alumina, ether–methanol (10%)]; IR (KBr disk) 3360, 3250 (br), 1670, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.26 (m, C1-H), 4.78 (br, NH_2), 3.40 (d, J = 2.0 Hz, C4-H's), 2.89 (s, NCH_3), 2.69–2.47 (m, pyrrolidine α-H's), 1.91–1.70 (m, pyrrolidine β-H's), 1.33 (d, J = 7.0 Hz, C1-CH_3); ^{13}C NMR ($CDCl_3$) δ 158.29 (C=O), 83.02 and 79.04 (acetylenic C's), 52.36 (pyrrolidine α-C's), 43.00 (C4), 42.35 (C1), 29.16 (NCH_3), 23.45 (pyrrolidine β-C's), 19.96 (C1-CH_3). Anal. ($C_{11}H_{19}N_3O$) C, H, N.

1-Methyl-1-[4-(1-pyrrolidinyl)-2-butynyl]urea (15). Compound **15** was prepared as described for **16** in 82% yield starting from the dioxalate salt of *N*-methyl-4-(1-pyrrolidinyl)-2-butynylamine (**56**)[3] (0.75 g, 2.24 mmol). Chromatographic purification was performed on an alumina column with chloroform followed by chloroform–methanol (5%) as eluents. The recrystallized sample had the following physical and spectral characteristics: mp 91–92 °C; TLC R_f = 0.23 [alumina, ether–methanol (10%)]; IR (KBr disk) 3410, 3200, 1660, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.02 (br, NH_2), 4.10 (t, J = 2.0 Hz, C1-H's), 3.40 (t, J = 2.0 Hz, C4-H's), 2.96 (s, CH_3), 2.75–2.42 (m, pyrrolidine α-H's), 1.91–1.68 (m, pyrrolidine β-H's); ^{13}C NMR ($CDCl_3$) δ 158.75 (C=O), 79.50 and 78.79 (acetylenic C's), 52.32 (pyrrolidine α-C's), 42.97 (C4), 37.72 (C1), 33.73 (CH_3), 23.39 (pyrrolidine β-C's). Anal. ($C_{10}H_{17}N_3O$) C, H, N.

General Procedure for Synthesis of 33, 34, 40, 48 and of Test Compounds 17, 18, 20, 22, and 23.[59] **Preparation of 1-(*tert*-Butoxycarbonyl)-3-[4-(1-pyrrolidinyl)-2-butynyl]-2,4-imidazolidinedione (40).** A solution of **39** (1.51 g, 6.34 mmol) in dioxane (8 mL) was added to a stirred mixture of pyrrolidine (0.54 g, 7.6 mmol), CuCl (0.05 g, 0.5 mmol), glacial acetic acid (0.12 g, 2.0 mmol), and paraformaldehyde (0.20 g, 6.67 mmol) in dioxane (10 mL). The mixture was heated to 50 °C (oil-bath temperature) for 4 h and then stirred at room temperature overnight. The dioxane was evaporated and the oily residue obtained was chromatographed on a silica column using chloroform–methanol (5→10%) as eluents. First eluted was a byproduct, 1,6-bis[1-(*tert*-butoxycarbonyl)-2,4-dioxoimidazolidin-3-yl]hexadiyne (**41**).[60] Further elution gave 1.70 g (81%) of **40** as a solid. An analytical sample of **40** was obtained after recrystallization from acetone–ether: mp 132–133.5 °C; TLC R_f = 0.40 [SiO_2, chloroform–methanol (10%)]; IR (KBr disk) 1805, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.32 (t, J = 2.0 Hz, C1-H's), 4.24 (ring CH_2C=O), 3.36 (t, J = 2.0 Hz, C4-H's), 2.69–2.45 (m, pyrrolidine α-H's), 1.90–1.68 (m, pyrrolidine β-H's), 1.56 [s, $C(CH_3)_3$]; ^{13}C NMR ($CDCl_3$) δ 166.49 (CH_2C=O), 150.99 and 148.27 (C=O's), 84.59 (C—O), 79.93 and 76.31 (acetylenic C's), 52.72 (pyrrolidine α-C's), 48.77 (ring CH_2C=O), 43.21 (C4), 28.51 (C1), 27.98 [$C(CH_3)_3$], 23.72 (pyrrolidine β-C's). Anal. ($C_{16}H_{23}N_3O_4$) C, H, N.

Pure **41** was obtained after a second purification on a silica column using ether as eluent. This gave 0.10 g (7%) of **41** as a solid. Trituration with *n*-pentane gave the analytical sample: mp 175–176.5 °C; TLC R_f = 0.38 (SiO_2, ether); IR (KBr disk) 1815, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.35 (s, 2 CH_2),[61] 4.26 (s, 2 ring CH_2),[61] 1.56 [s, 2 $C(CH_3)_3$]; ^{13}C NMR ($CDCl_3$) δ 166.16 (2 ring CH_2C=O), 150.60 and 148.06 (C=O's), 84.60 (2 C—O), 71.29 (2 C2),[38] 67.55 (2 C3),[38] 48.74 (2 ring CH_2), 28.51 (2 C1), 27.83 [2 $C(CH_3)_3$]. Anal. ($C_{22}H_{26}N_4O_8$) C, H, N.

General Procedure for N-Deprotection of *t*-Boc Derivatives 33, 34, 40, 41, and 48.[59] **Preparation of 3-[4-(1-Pyrrolidinyl)-2-butynyl]-2,4-imidazolidinedione (24).** A mixture of trifluoroacetic acid (10 mL) in dichloromethane (10 mL) was added to a stirred solution of **40** (1.48 g, 4.59 mmol) in dichloromethane (20 mL) at 0 °C (ice bath). The ice bath was removed after 15 min and the mixture was stirred for 3.5 h at room temperature. The mixture was alkalinized by addition of aqueous 10% K_2CO_3 (175 mL) and was then extracted with dichloromethane (4 × 175 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated in vacuo. The residue was dissolved in a small volume of dichloromethane–methanol (2.5%) and chromatographed on an alumina column using ether followed by ether–methanol (5%) as eluents. This gave 0.82 g (80%) of **24** as a white solid: mp 137–138.5 °C. The base was converted into the oxalate and recrystallized (Table I): TLC R_f = 0.30 [free base on alumina, ether–methanol (10%)]; IR (free base, KBr disk) 3280, 1755, 1710 cm^{-1}; ^1H NMR (oxalate, D_2O) δ 4.22 (t, J = 2.2 Hz, 2 H), 3.95 (s, ring CH_2C=O), 3.92 (t, partially obscured, J = 1.7 Hz, 2 H), 3.70–3.30 (m, pyrrolidine H's, 2 H), 3.30–2.85 (m, pyrrolidine H's, 2 H), 2.11–1.73 (m, pyrrolidine H's, 4 H); ^{13}C NMR (oxalate, D_2O) δ 175.29 (CH_2C=O), 166.70 (oxalate C=O's), 159.76 (NCON), 83.81 (C2), 73.93 (C3), 54.97 (pyrrolidine α-C's), 48.11 (ring CH_2C=O), 44.78 (C4), 29.09 (C1), 24.52 (pyrrolidine β-C's).

1,6-Bis(2,4-dioxoimidazolidin-3-yl)hexadiyne (42). Compound **41** (0.35 g, 0.74 mmol) was N-deprotected by the method described above for **40**. The crude acidic mixture was concentrated directly in vacuo. The solid residue obtained was triturated with methanol–ether to give 79 mg (39%)[62] of **42**: mp 212–214 °C; IR (KBr disk) 3250, 1780, 1720 (br) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.21 (s, 2 NH), 4.27 (s, 2 ring CH_2), 3.96 (s, 2 CH_2); ^{13}C NMR (DMSO-d_6) δ 170.92 (2 CH_2C=O), 155.98 (2 NCON), 73.74 (2 C2), 65.72 (2 C3), 45.95 (2 CH_2C=O), 27.35 (2 C1). Anal. ($C_{12}H_{10}N_4O_4 \cdot 0.25H_2O$) C, H, N.

Pharmacology. Guinea Pig Ileum. A standard guinea pig ileum was set up in Tyrode's solution (pH 7.4) as described previously.[63] The Tyrode's solution contained hexamethonium (0.3 mM). Ileal contractions were recorded isotonically at 1 g of tension with an electromechanical displacement transducer and a potentiometric recorder. Concentration–response curves to

(58) These assignments were based on literature data given in ref 39a.

(59) See Table I for chromatographic conditions.

(60) Compound **41** was also obtained by treating **39** with CuCl (0.3 equiv) and triethylamine (1.12 equiv) in dioxane at 60 °C for 3.5 h. The yield of **41** after column chromatography was 88%.

(61) Assignments could be reversed.

(62) An additional fraction (55 mg) of **42** which contained minor impurities (^1H NMR) was also obtained.

(63) Ringdahl, B. Determination of Dissociation Constants and Relative Efficacies of Oxotremorine Analogs at Muscarinic Receptors in the Guinea Pig Ileum by Pharmacological Procedures. *J. Pharmacol. Exp. Ther.* **1984**, *229*, 199–206.

carbachol were constructed by the cumulative dose–response technique by increasing stepwise its concentration by a factor of 2.15.

Spasmogenic activity (EC_{50}) was estimated by nonlinear regression analysis (BMDP Statistical Software; Los Angeles, CA). Dose–response data were fitted to the following equation: $Y = E_{max}/(1 + (X/EC_{50})^N$, where Y is the percent contraction produced at each agonist concentration, E_{max} is the maximal contraction attainable by each agonist, X is the concentration of agonist added to the bath, EC_{50} is the concentration producing half-maximal contraction, and N is the slope factor. E_{max} values were determined relative to carbachol. Dissociation constants (K_D) for antagonists were estimated with carbachol as the agonist.[64] Antagonists (i.e., **16** and **21**) equilibrated with the tissue for 20 min prior to the addition of carbachol.

Relative efficacies and K_D values for the full agonists on the ileum were determined by irreversibly reducing the muscarinic receptor population by alkylation with propylbenzilylcholine mustard (PrBCM).[63] The following concentrations of PrBCM were used in the ileal assay (compound number in parentheses): 5–10 nM (**17–19**); 20–40 nM (**20**, **22**); 1–6 μM (**1**, carbachol). For partial agonists, relative efficacies and K_D were determined by comparison of their concentration–response curves with that of carbachol as described previously.[63]

Muscarinic Receptor Binding Assay. Binding assays were performed using the filtration method described by Yamamura and Snyder.[65] Rat cerebral cortex was suspended in 40 volumes of 0.32 M sucrose and homogenized in a glass homogenizer tube with a Teflon pestle (10 strokes). The homogenates were centrifuged at 1000g for 10 min at 4 °C, and the pellet was discarded. The supernatant was spun at 30000g for 20 min. This pellet was then resuspended in 50 mM sodium–potassium phosphate buffer (pH 7.4) to a concentration of 20 mg wet weight/mL buffer. Prior to performing the assay, the tissue stock-suspension was finally diluted to 2 mg of tissue/mL. Saturation studies (2 mL total volume) were conducted by incubating [^{3}H]-3-quinuclidinyl benzilate ([^{3}H]QNB: 43 Ci/mmol); New England Nuclear; 0.003–1.0 nM) with the cortical homogenate (0.1 mL; 30–60 μg of protein) in the absence or presence of 10 mM atropine. For competition experiments, the homogenate (0.1 mL) was incubated with nonlabeled ligand (0.1 mL) and [^{3}H]QNB (0.3 nM) in a total volume of 2 mL of 50 mM phosphate buffer. Nondisplaceable binding measured in the presence of 10 μM atropine was defined as nonspecific. All binding assays were performed in triplicate and equilibrated for 120 min at 30 °C. Rapid vacuum filtration across glass fiber filters (Whatman, GF/B) was used to separate bound and free radioligand. IC_{50} values (concentration of ligand which reduced maximal specific [^{3}H]QNB binding by 50%) were also obtained by fitting the data to a one-site binding model by nonlinear regression analysis.[66] The IC_{50} values were corrected for receptor occupancy by [^{3}H]QNB as described by Cheng and Prusoff[67] to give K_i values (concentration of ligand that causes half-maximal receptor occupancy in the absence of [^{3}H]QNB). Protein was determined by the method of Lowry et al.[68] using albumin as the standard. Saturation studies showed that [^{3}H]-QNB has a $K_D = 0.18 \pm 0.03$ nM and a $B_{max} = 478 \pm 50$ fmol/mg protein ($N = 4$).

Acknowledgment. Support for this study was provided by grants from the Swedish Natural Science Research Council and United States Public Health Service (Grants No. GM-37816 and MH-17691).

Registry No. **15**, 142237-90-9; **15**·free base, 142237-89-6; **16**, 142237-92-1; **16**·free base, 142237-91-0; **17**, 133989-32-9; **17**·free base, 133989-44-3; **18**, 142237-94-3; **18**·free base, 142237-93-2; **19**, 142237-95-4; **19**·free base, 131422-31-6; **20**, 131422-22-5; **20**·free base, 131422-21-4; **21**, 131422-68-9; **21**·free base, 131422-67-8; **22**, 142237-97-6; **22**·free base, 142237-96-5; **23**, 142237-99-8; **23**·free base, 142237-98-7; **24**, 142238-01-5; **24**·free base, 142238-00-4; **25**, 142238-02-6; **26**, 142238-03-7; **27**, 131423-07-9; **28**, 131423-09-1; **29**, 131423-06-8; **30**, 142238-04-8; **31**, 142238-05-9; **32**, 142238-06-0; **33**, 131422-29-2; **34**, 142238-07-1; **35**, 142238-08-2; **36**, 142238-09-3; **37**, 2718-05-0; **38**, 142238-10-6; **39**, 142238-11-7; **40**, 142238-12-8; **41**, 142238-13-9; **42**, 142238-14-0; **43**, 133989-43-2; **44**, 142238-15-1; **45**, 142238-16-2; **46**, 142238-17-3; **47**, 142238-18-4; **48**, 142238-19-5; **49**, 24138-94-1; **50**, 142259-36-7; **51**, 142238-20-8; **52**, 41731-11-7; **53**, 142238-21-9; **54**, 111903-44-7; **55**, 111903-46-9; **56**, 75858-55-8; **57**, 142238-22-0; propargylamine, 2450-71-7; 1-methyl-2-propynylamine hydrochloride, 42105-26-0; 2,4-imidazolidinedione, 461-72-3; 2-chloroethyl isocyanate, 1943-83-5; propargyl bromide, 106-96-7; 1,3-dimethylurea, 96-31-1; 1-methyl-2-propynyl p-toluenesulfonate, 53487-52-8.

Supplementary Material Available: ^{1}H NMR spectral data for **15–23**, **33**, **34**, **46–48**, **50**, and **51**, ^{13}C NMR spectral data for **15–23**, **27** (in CD_3OD), **50**, and **51**, and IR spectral data for **15–24**, **50**, and **51** (5 pages). Ordering information is given on any current masthead page.

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