

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

Björn M. Nilsson,<sup>†</sup> Hugo M. Vargas,<sup>‡</sup> and Uli Hacksell\*<sup>†</sup>

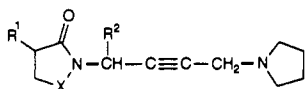
Department of Organic Pharmaceutical Chemistry, Uppsala Biomedical Center, University of Uppsala, Box 574, S-751 23 Uppsala, Sweden, and Department of Pharmacology, School of Medicine, University of California, Los Angeles, California 90024. Received December 26, 1991

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 [<sup>3</sup>H]-3-quinuclidinyl benzilate ([<sup>3</sup>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)<sup>1</sup> have resulted in muscarinic antagonists.<sup>2,3</sup> Among the more potent of these antimuscarinic agents are the 5-methyl substituted pyrrolidone 2 and the C1-methyl substituted derivative 8.<sup>2b</sup> Compound 2 shows 12-fold higher affinity for ileal M<sub>3</sub><sup>4,5</sup> muscarinic receptors than 1. In addition, 2 behaves as a potent tremorolytic<sup>6</sup> and antihypertensive<sup>7</sup> 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<sub>1</sub> muscarinic receptors than at M<sub>3</sub> receptors in vitro.<sup>8</sup>

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.<sup>8</sup> The *N*-1 unsubstituted pyrazolidone analogue 3 was an agonist at ileal M<sub>3</sub> and at ganglionic M<sub>1</sub> muscarinic receptors with lower (30- and 50-fold, respectively) potency than 1. As observed for 1, compound 3 displayed low M<sub>1</sub>/M<sub>3</sub> receptor subtype selectivity in vitro. However, the *N*-formyl derivative 4, which was an antagonist, showed approximately 500-fold higher affinity for ganglionic M<sub>1</sub> receptors than for ileal M<sub>3</sub> receptors. The *N*-acetyl compound 5 was also an antagonist but displayed almost no M<sub>1</sub>/M<sub>3</sub> receptor subtype selectivity.<sup>8</sup>



- 1: R<sup>1</sup> = H; X = CH<sub>2</sub>; R<sup>2</sup> = H
- 2: R<sup>1</sup> = H; X = CHCH<sub>3</sub>; R<sup>2</sup> = H
- 3: R<sup>1</sup> = H; X = NH; R<sup>2</sup> = H
- 4: R<sup>1</sup> = H; X = NCHO; R<sup>2</sup> = H
- 5: R<sup>1</sup> = H; X = NCOCH<sub>3</sub>; R<sup>2</sup> = H
- 6: R<sup>1</sup> = CH<sub>3</sub>; X = CH<sub>2</sub>; R<sup>2</sup> = H
- 7: R<sup>1</sup> = H; X = CO; R<sup>2</sup> = H
- 8: R<sup>1</sup> = H; X = CH<sub>2</sub>; R<sup>2</sup> = CH<sub>3</sub>

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.<sup>2,6</sup> 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).<sup>9</sup> 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.<sup>10</sup> Development of new muscarinic agonists that

- (1) Cho, A.; Haslett, W. L.; Jenden, D. J. The Identification of an Active Metabolite of Tremorine. *J. Biochem. Res. Commun.* 1961, 5, 276–279.
- (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<sub>2</sub> "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<sub>1</sub>, M<sub>2</sub> and M<sub>3</sub> 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 Vasodilation. *J. Pharmacol. Exp. Ther.* 1990, 253, 165–170.
- (8) Amstutz, R.; Clossé, 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.

<sup>†</sup>University of Uppsala.

<sup>‡</sup>University of California.

Table I. Physical Data of the New Compounds Tested<sup>a</sup>

compd	yield	TLC, $R_f^{b,c}$	mp (°C)	formula <sup>d,e</sup>
15	82	0.23 (A)	132–134	C <sub>10</sub> H <sub>17</sub> N <sub>3</sub> O·1.5C <sub>2</sub> H <sub>2</sub> O <sub>4</sub>
16	80	0.33 (A)	114–116	C <sub>11</sub> H <sub>19</sub> N <sub>3</sub> O·C <sub>2</sub> H <sub>4</sub> O <sub>4</sub>
17	83	0.13 (B)	122–124	C <sub>11</sub> H <sub>19</sub> N <sub>3</sub> O·HCl
18	86	0.19 (B)	131–132	C <sub>12</sub> H <sub>21</sub> N <sub>3</sub> O·C <sub>2</sub> H <sub>2</sub> O <sub>4</sub>
19	55 <sup>f,g</sup>	0.15 (C)	132–133	C <sub>11</sub> H <sub>17</sub> N <sub>3</sub> O·C <sub>2</sub> H <sub>2</sub> O <sub>4</sub>
20	88	0.42 (C)	121.5–122.5	C <sub>12</sub> H <sub>19</sub> N <sub>3</sub> O·C <sub>2</sub> H <sub>2</sub> O <sub>4</sub>
21	59 <sup>h,i</sup>	0.30 (C)	151–152	C <sub>12</sub> H <sub>19</sub> N <sub>3</sub> O·C <sub>2</sub> H <sub>2</sub> O <sub>4</sub>
22	78	0.14 (D)	119–120	C <sub>12</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> ·C <sub>2</sub> H <sub>2</sub> O <sub>4</sub>
23	100	0.52 (C)	136.5–138	C <sub>13</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub> ·C <sub>2</sub> H <sub>2</sub> O <sub>4</sub>
24	65 <sup>j</sup>	0.30 (A)	174–176	C <sub>11</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> ·C <sub>2</sub> H <sub>2</sub> O <sub>4</sub>

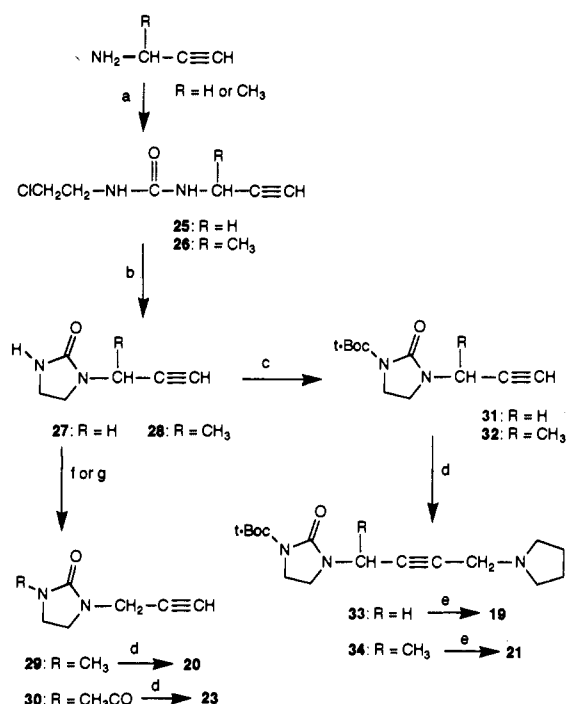
<sup>a</sup> For details of their preparation, see the Experimental Section.

<sup>b</sup>  $R_f$  values correspond to the free bases. <sup>c</sup> A: alumina [ether-methanol (10%)]. B: silica [chloroform-methanol (10%)]. C: alumina [ether-methanol (5%)]. D: silica (acetone). <sup>d</sup> All compounds were analyzed for C, H, and N. The analytical results obtained were within  $\pm 0.4\%$ . <sup>e</sup> 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. <sup>f</sup> Overall yield from 31. <sup>g</sup> The *N*-*t*-Boc protected precursor 33 was chromatographed on an alumina column using ether as eluent. <sup>h</sup> Overall yield from 32. <sup>i</sup> The *N*-*t*-Boc protected precursor 34 was chromatographed on a silica column using chloroform-methanol (5%) as eluent. <sup>j</sup> Overall yield from 39.

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

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.<sup>16</sup> We have thus prepared and tested pharmacologically a series of *N*-substituted 2-imidazolidones (19–23) and a hydantoin analogue (24).<sup>17</sup>

- 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.
- 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.
- (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 Acetylcholine Turnover and Muscarinic Receptor Binding in Rat Brain. *Neurosci. Abstr.* 1991, 17, 389.
- 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.
- 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.
- 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.

Scheme I<sup>a</sup>

<sup>a</sup> Reagents: (a) 2-chloroethyl isocyanate, Et<sub>3</sub>N (cat.), THF or CH<sub>3</sub>CN; (b) pulverized KOH, Bu<sub>4</sub>NBr (0.2 equiv), THF; (c) di-*tert*-butyl dicarbonate, 4-DMAP, CH<sub>3</sub>CN; (d) pyrrolidine, (HCHO)<sub>n</sub>, CuCl, HOAc, dioxane; (e) CF<sub>3</sub>COOH, CH<sub>2</sub>Cl<sub>2</sub>, 0 → 20 °C; (f) NaH, MeI, THF, 0 → 20 °C; (g) AcCl, Et<sub>3</sub>N, ether, 0 → 20 °C.

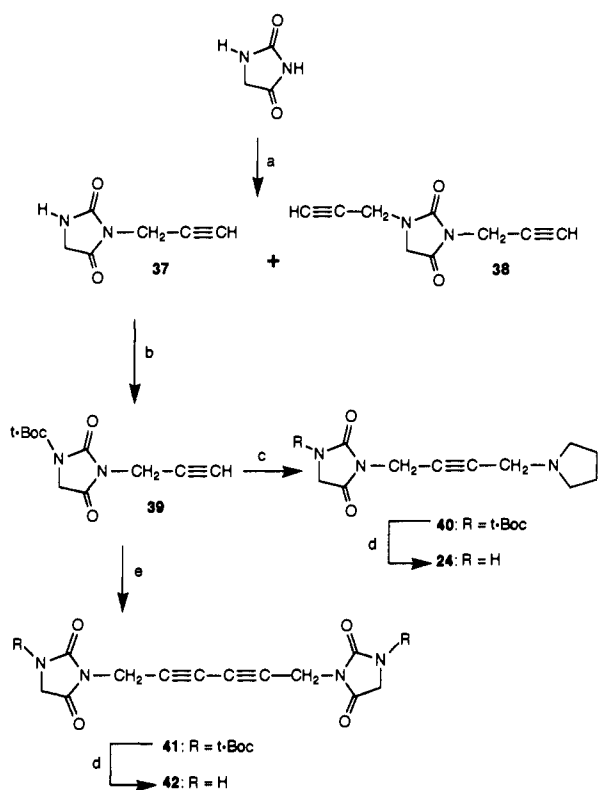
The *N*-methylacetamido analogue 9 (UH-5)<sup>2b,18</sup> is a muscarinic agonist with pharmacological properties similar to that of 1. It has 2–3-fold lower affinity to ileal M<sub>3</sub> receptors than 1, but displays slightly higher efficacy than 1.<sup>2b,18</sup> Similarly, the propionamide homologues of 9 (i.e., 11) and 10 (i.e., 12) retained considerable muscarinic agonist activity on the ileum.<sup>2b</sup> Further methyl substitution at the  $\alpha$ -carbon of 9, giving 13,<sup>2b</sup> resulted in an antagonist whereas the isosteric *N,N*-dimethylurea derivative 14 has been reported<sup>17b,18a</sup> 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 [<sup>3</sup>H]-3-quinuclidinyl benzilate ([<sup>3</sup>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.

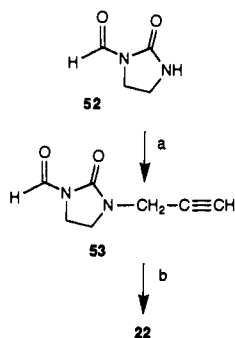
## Chemistry

The synthetic procedures employed are outlined in

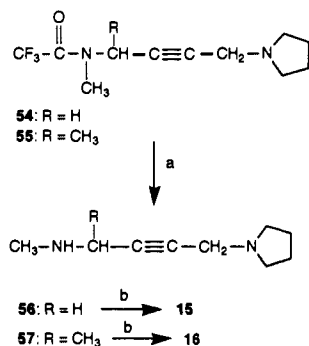
- During the preparation of this manuscript, reports have appeared which include the synthesis and the muscarinic activity of 19–21: (a) Moon, M. W.; Heier, R. F. International Patent N:o WO 90/04588, 1990. Compare: *Chem. Abstr.* 1991, 114, 42786p. (b) Moon, M. W.; Chidester, C. G.; Heier, R. F.; Morris, 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.
- (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. Acetylenic Compounds of Potential Pharmacological Value. XXV. *N*-(4-Pyrrolidino-2-butynyl)-*N*-alkylcarboxamides. *Acta Pharm. Suec.* 1978, 15, 67–70.

Scheme II<sup>a</sup>

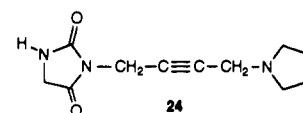
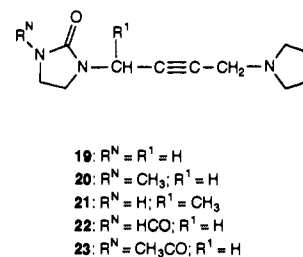
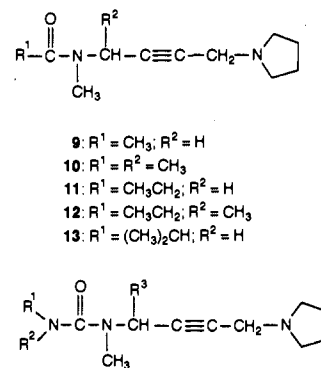
<sup>a</sup> Reagents: (a) propargyl bromide, pulverized KOH,  $\text{Bu}_4\text{NBr}$  (0.1 equiv), THF,  $0^\circ\text{C} \rightarrow \text{reflux}$ ; (b) di-*tert*-butyl dicarbonate, 4-DMAP,  $\text{CH}_3\text{CN}$ ; (c) pyrrolidine,  $(\text{HCHO})_n$ ,  $\text{CuCl}$ , HOAc, dioxane; (d)  $\text{CF}_3\text{COOH}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0 \rightarrow 20^\circ\text{C}$ ; (e)  $\text{CuCl}$  (0.3 equiv),  $\text{Et}_3\text{N}$ , dioxane.

Scheme III<sup>a</sup>

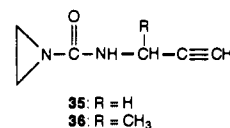
<sup>a</sup> Reagents: (a) NaH, propargyl bromide, THF,  $70^\circ\text{C}$ ; (b) pyrrolidine,  $(\text{HCHO})_n$ ,  $\text{CuCl}$ , HOAc, dioxane.

Scheme IV<sup>a</sup>

<sup>a</sup> Reagents: (a) 5 M NaOH; (b) KOCN, HOAc,  $\text{H}_2\text{O}/\text{THF}$ ,  $70^\circ\text{C}$ .



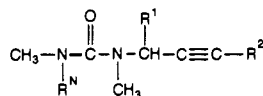
Schemes I-IV. Physical data of the test compounds 15-24 are collected in Table I. The 2-imidazolidinones 27<sup>19</sup> and 28<sup>20</sup> were prepared in 82 and 72% yield, respectively, by cyclization of the 2-chloroethylureas 25 and 26, using powdered KOH in the presence of  $\text{Bu}_4\text{NBr}$  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.



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

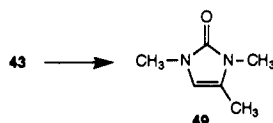
*N*-Alkylation of 2,4-imidazolidinedione with propargyl bromide and 1,3-dimethylurea with propargyl bromide or 1-methyl-2-propynyl *p*-toluenesulfonate,<sup>23</sup> by use of pow-

- (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:  $\text{R}^N = \text{R}^1 = \text{R}^2 = \text{H}$   
 44:  $\text{R}^N = \text{CH}_2-\text{C}\equiv\text{CH}$ ;  $\text{R}^1 = \text{R}^2 = \text{H}$   
 45:  $\text{R}^N = \text{H}$ ;  $\text{R}^1 = \text{CH}_3$ ;  $\text{R}^2 = \text{H}$   
 46:  $\text{R}^N = t\text{-Boc}$ ;  $\text{R}^1 = \text{R}^2 = \text{H}$   
 47:  $\text{R}^N = t\text{-Boc}$ ;  $\text{R}^1 = \text{CH}_3$ ;  $\text{R}^2 = \text{H}$   
 48:  $\text{R}^N = t\text{-Boc}$ ;  $\text{R}^1 = \text{H}$ ;  $\text{R}^2 = \text{CH}_2\text{NC}_4\text{H}_9$

dered KOH in the presence of  $\text{Bu}_4\text{NBr}$  in THF, gave the *N*-alkylated hydantoin 37<sup>24</sup> (Scheme II) and the urea derivatives 43 and 45 in isolated yields of 52, 20,<sup>25</sup> 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.<sup>26</sup> 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.<sup>27,28</sup>



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

- (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*-Propinylbenzamidin. *Arch. Pharm.* 1966, 299, 107-112.
- (25) Changing solvent to  $\text{CH}_3\text{CN}$  and/or omitting the phase-transfer catalyst did not influence the yield of 43. Similarly, running the reaction at  $-78 \rightarrow 22^\circ\text{C}$  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  $R_f = 0.30$  [ $\text{SiO}_2$ , ether-methanol (10%)].  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, and IR spectral data of 49 were in agreement with those reported.<sup>29</sup> 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.

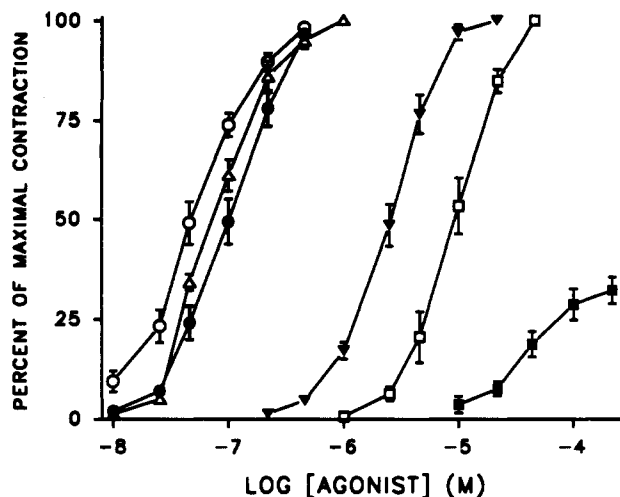


Figure 1. Concentration-response curves of compounds 1 (O), 20 ( $\Delta$ ), carbachol ( $\bullet$ ), 17 ( $\blacktriangledown$ ), 15 ( $\square$ ), and 24 ( $\blacksquare$ ) on the isolated guinea pig ileum. Values are means and vertical bars show SE. Number of preparations used are given in Table II.

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<sup>30</sup> and 2-imidazolidones.<sup>31,32</sup> 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<sup>33</sup> 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,<sup>34</sup> 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<sup>35</sup> of the terminal acetylenic precursors. The

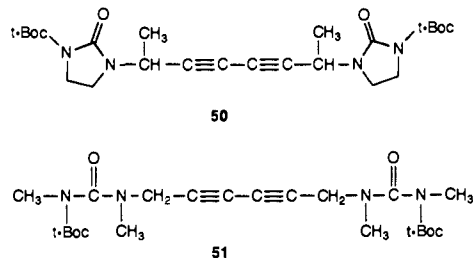
- (30) Bombardieri, C. C.; Taurins, A. The Mannich Condensation of Compounds Containing Acidic Imino Groups. *Can. J. Chem.* 1955, 33, 923-928.
- (31) Trippetta, L.; Orazi, O. O.; Corral, R. A. Sustitucion en el Anillo Hidantoinico y Sistemas Relacionados. Parte IV: Aminometilacion de Acidos Parabenicos y Etilenurea. *An. Assoc. 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<sup>a</sup>

compd	N <sup>b</sup>	guinea pig ileum				rat cerebral cortex
		EC <sub>50</sub> , <sup>c,d</sup> μM	K <sub>D</sub> , <sup>e,f</sup>	E <sub>max</sub> , <sup>g</sup>	efficacy <sup>h</sup>	[ <sup>3</sup> H]QNB displacement, K <sub>i</sub> (μM) <sup>i</sup>
1 (oxotremorine)	6	0.05 ± 0.004	1.2 ± 0.1	1.0	1.0	0.23 ± 0.06
6 <sup>j</sup>		0.50 ± 0.03	11.5 ± 2.6	1.0	0.10	
8 <sup>k</sup>		0	0.091 ± 0.01	0	0	0.059 ± 0.001
10		0.19 ± 0.03 <sup>l</sup>	0.24 ± 0.07 <sup>l</sup>	0.83 <sup>l</sup>	0.013 <sup>l</sup>	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 <sup>m</sup>	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 <sup>m</sup>	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	

<sup>a</sup> Values are means plus or minus standard errors. <sup>b</sup> Number of ileal preparations used. <sup>c</sup> The concentration of an agonist or partial agonist that elicits 50% of its own maximum contractile response. <sup>d</sup> The reported EC<sub>50</sub> values are 1.0, 0.07, 0.42, and 0.42 μM for 7, 9, 11, and 12, respectively (ref 2b). <sup>e</sup> Dissociation constant of the drug-receptor complex. <sup>f</sup> The reported K<sub>D</sub> values are 5.4 and 2.2 μM for 7 and 9, respectively (ref 2b). <sup>g</sup> The maximum contractile response relative to that elicited by carbachol. <sup>h</sup> Relative efficacies were determined with oxotremorine as the reference. <sup>i</sup> K<sub>i</sub> 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. <sup>j</sup> Values are from ref 69. <sup>k</sup> Values are from ref 70. <sup>l</sup> Values are from ref 71. <sup>m</sup> These compounds were competitive antagonists; the Schild slopes were equivalent to 1.

isolated yields were 37%,<sup>36</sup> 7%, and 25%,<sup>37</sup> 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, <sup>1</sup>H, and <sup>13</sup>C NMR<sup>38</sup>) 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.



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

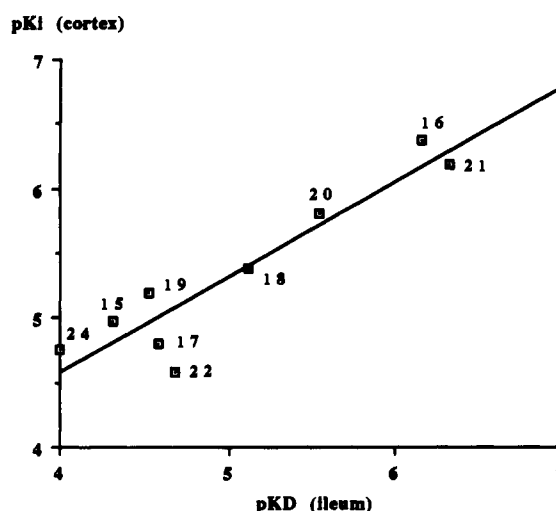


Figure 2. Relationship between dissociation constants ( $-\log K_D$ ) at ileal muscarinic receptors and inhibition of [<sup>3</sup>H]QNB binding to homogenates of rat cerebral cortex ( $-\log K_i$ ) for the new analogues. Values are from Table II. The regression line is described by  $pK_i(\text{cortex})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

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<sup>21</sup> by basic hydrolysis (5 M NaOH) as previously described for the synthesis of 56<sup>3</sup> from trifluoroacetamide 54<sup>21</sup> (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<sup>40</sup> 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. <sup>1</sup>H and <sup>13</sup>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. <sup>1</sup>H and <sup>13</sup>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.

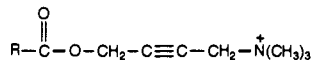
- (40) Compare ref 24b and Yura, Y. *Studies on Acetylenic Compounds*. XXV. Ringclosure. (5). New Synthetic Methods of Heterocyclic Compounds from  $\alpha$ -Amino- and  $\alpha$ -N-substituted Aminoacetylenic Compounds. *Chem. Pharm. Bull.* 1962, **10**, 1087–1093.

fumarate salts, respectively.<sup>41,42</sup>

### 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 [<sup>3</sup>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.<sup>2b</sup> 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  $\alpha$  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.<sup>2b</sup> 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.<sup>43</sup>



58: R = CH<sub>3</sub>  
59: R = NH<sub>2</sub>

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.<sup>44</sup>

It has been observed previously<sup>2b</sup> that the intrinsic muscarinic activity at ileal  $M_3$  receptors is preserved when a methyl group is introduced  $\alpha$  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,<sup>6</sup> 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.<sup>44</sup> 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,<sup>2b</sup> 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  $\mu$ M 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.<sup>45</sup> 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<sub>2</sub> 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.<sup>46</sup> 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) <sup>1</sup>H and <sup>13</sup>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.<sup>46,47</sup> 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. <sup>1</sup>H and <sup>13</sup>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 <sup>1</sup>H and <sup>13</sup>C NMR spectra of the oxalate salts of 18 and 24. Assignments of <sup>13</sup>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<sub>2</sub>. Thin-layer chromatography was carried out on aluminum sheets precoated with silica gel 60 F<sub>254</sub> (0.2 mm) or aluminum oxide 60 F<sub>254</sub> 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<sub>4</sub> spraying (or UV detection; 49). The elemental analyses were performed by Mikro Kemi AB, Uppsala, Sweden, or Analytische Laboratorien, Gummiesbach, 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<sup>49</sup> (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*<sub>f</sub> = 0.55 (SiO<sub>2</sub>, ether); IR (KBr disk) 3320, 3280, 1620, 1580 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 5.91–5.51 (m, 2 NH), 4.81–4.37 (m, C1-H), 3.79–3.41 (m, CH<sub>2</sub>CH<sub>2</sub>), 2.28 (d, *J* = 2.4 Hz, C3-H), 1.42 (d, *J* = 7.0 Hz, C1-CH<sub>3</sub>); <sup>13</sup>C NMR (CD<sub>3</sub>OD) δ 159.42 (C=O), 85.89 (C2), 71.03 (C3), 44.84 and 42.90 (CH<sub>2</sub>'s), 38.39 (C1), 22.95 (C1-CH<sub>3</sub>). Anal. (C<sub>7</sub>H<sub>11</sub>ClN<sub>2</sub>O) 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*<sub>f</sub> = 0.42 (SiO<sub>2</sub>, ether); IR (KBr disk) 3330, 3285, 1620 (br) cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 3.89 (d, *J* = 2.4 Hz, C1-H's), 3.68–3.33 (m, CH<sub>2</sub>CH<sub>2</sub>), 2.54 (t, *J* = 2.4 Hz, C3-H); <sup>13</sup>C NMR (CD<sub>3</sub>OD) δ 160.01 (C=O), 81.69 (C2), 71.71 (C3), 44.75 and 42.93 (C1CH<sub>2</sub>CH<sub>2</sub>N), 30.14 (C1). Anal. (C<sub>6</sub>H<sub>9</sub>ClN<sub>2</sub>O) C, H, N.

**N-(1-Methyl-2-propynyl)-2-imidazolidone (28).**<sup>20</sup> Bu<sub>4</sub>NBr (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.<sup>17a</sup> mp 90–92 °C); TLC *R*<sub>f</sub> = 0.43 [SiO<sub>2</sub>, ether-methanol (5%)]; IR<sup>50</sup> (KBr disk) 3260, 3235, 2105, 1695 (br) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 5.92 (br, NH), 4.83 (qd, *J* = 7.2 and 2.4 Hz, C1-H), 3.71–3.32 (m, ring CH<sub>2</sub>'s), 2.29 (d, *J* = 2.2 Hz, C3-H), 1.38 (d, *J* = 7.2 Hz, C1-CH<sub>3</sub>); <sup>13</sup>C NMR<sup>51</sup> (CDCl<sub>3</sub>) δ 162.05 (C=O), 81.97 (C2), 71.50 (C3), 40.31 (ring CH<sub>2</sub>'s), 39.69 (C1), 37.96 (ring CH<sub>2</sub>'s), 19.53 (C1-CH<sub>3</sub>). Anal. (C<sub>7</sub>H<sub>10</sub>N<sub>2</sub>O) 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*<sub>f</sub> = 0.60 [SiO<sub>2</sub>, ether-methanol (5%)]; IR (KBr disk) 3240, 2115, 1685 (br), 1540 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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<sub>2</sub>'s), 1.34 (d, *J* = 7.0 Hz, C1-CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 164.03 (C=O), 84.01 (C2), 70.24 (C3), 37.96 (C1), 26.14 (ring CH<sub>2</sub>'s), 22.06 (C1-CH<sub>3</sub>). Anal. (C<sub>7</sub>H<sub>10</sub>N<sub>2</sub>O) C, H, N.

***N*-(2-Propynyl)-2-imidazolidone (27).**<sup>17b</sup> 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.<sup>17b</sup> mp 123–125 °C); TLC *R*<sub>f</sub> = 0.33 [SiO<sub>2</sub>, ether-methanol (5%)]; IR (KBr disk) 3260, 3220 (shoulder), 2110, 1680 (br) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 5.68 (br, NH), 4.01 (d, *J* = 2.6 Hz, C1-H's), 3.62–3.35 (m, ring CH<sub>2</sub>'s), 2.25 (t, *J* = 2.6 Hz, C3-H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 162.42 (C=O), 78.02 (C2), 72.12 (C3), 44.30 and 37.90 (ring CH<sub>2</sub>'s), 33.24 (C1). Anal. (C<sub>6</sub>H<sub>8</sub>N<sub>2</sub>O) 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: <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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<sub>2</sub>'s); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 164.74 (C=O), 79.53 (C2), 71.13 (C3), 30.03 (C1), 25.95 (ring CH<sub>2</sub>'s).

**1-Methyl-3-(2-propynyl)-2-imidazolidone (29).**<sup>17b,52</sup> 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.<sup>17b</sup> mp 57–59 °C); TLC *R*<sub>f</sub> = 0.30 (SiO<sub>2</sub>, ether); IR (KBr disk) 3220, 2100, 1690 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.00 (d, *J* = 2.6 Hz, C1-H's), 3.43–3.31 (m, ring CH<sub>2</sub>'s), 2.80 (s, CH<sub>3</sub>), 2.28 (t, *J* = 2.4 Hz, C3-H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 160.48 (C=O), 77.99 (C2), 72.00 (C3), 44.51 and 41.64 (ring CH<sub>2</sub>'s), 33.79 (C1), 30.89 (CH<sub>3</sub>). Anal. (C<sub>7</sub>H<sub>10</sub>N<sub>2</sub>O) 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<sub>3</sub> solution (300 mL) and stirred for 1 h at room temperature. Extraction with ether (6 × 125 mL), drying (MgSO<sub>4</sub>) 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<sup>48</sup> 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 à 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 <sup>13</sup>C NMR spectral data of 2-imidazolidones, see: Flaster, H.; Kohn, H. Syntheses and Spectral Properties of 2-Thio-biotin 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<sub>2</sub>, ether); IR (KBr disk) 3200, 2100, 1725 (ring C=O),<sup>53</sup> 1670 (CH<sub>3</sub>C=O)<sup>53</sup> cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.11 (d,  $J$  = 2.4 Hz, C1-H's), 3.99–3.42 (m, ring CH<sub>2</sub>'s), 2.49 (s, CH<sub>3</sub>), 2.37 (t,  $J$  = 2.6 Hz, C3-H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 170.27 (CH<sub>3</sub>CO), 154.09 (NCON), 76.69 (C2), 72.92 (C3), 39.82 and 39.14 (ring CH<sub>2</sub>'s), 33.02 (C1), 23.02 (CH<sub>3</sub>). Anal. (C<sub>8</sub>H<sub>10</sub>N<sub>2</sub>O) C, H, N.

**3-(2-Propynyl)-2,4-imidazolidinedione (37).**<sup>24</sup> Bu<sub>4</sub>NBr (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<sub>2</sub>, ether); IR (KBr, disk) 3225, 2120, 1770, 1705 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.28 and 4.26 (overlapping d's,  $J$ 's = 2.4 Hz, 2 CH<sub>2</sub>C≡CH), 4.03 (s, ring CH<sub>2</sub>), 2.41 and 2.28 (t's,  $J$ 's = 2.4 Hz, 2 C≡CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 168.20 (CH<sub>2</sub>C=O), 154.70 (NCON), 76.54 and 76.26 (2 C≡CH), 73.82 and 71.63 (2 C≡CH), 48.77 (ring CH<sub>2</sub>), 32.16 and 27.90 (2 CH<sub>2</sub>C≡CH). Anal. (C<sub>9</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>) 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,<sup>24a</sup> 186–187 °C<sup>24b</sup>); TLC  $R_f$  = 0.47 [SiO<sub>2</sub>, ether-methanol (5%)]; IR<sup>54</sup> (KBr disk) 3260, 3200 (br), 2120, 1770, 1715 (br) cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 4.23 (d,  $J$  = 2.6 Hz, C1-H's), 3.98 (s, ring CH<sub>2</sub>), 2.62 (t,  $J$  = 2.4 Hz, C3-H); <sup>13</sup>C NMR<sup>55</sup> (CD<sub>3</sub>OD) δ 172.89 (CH<sub>2</sub>C=O), 158.71 (NCON), 78.29 (C2), 72.45 (C3), 47.40 (ring CH<sub>2</sub>), 28.13 (C1). Anal. (C<sub>8</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>) 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<sub>4</sub>NBr (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<sub>2</sub>, ether-methanol (5%)]; IR (KBr disk) 3385, 3250, 2110, 1630, 1545 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.85 (br, NH), 4.12 (d,  $J$  = 2.4 Hz, C1-H's), 2.94 (s, CONCH<sub>3</sub>), 2.81 (d,  $J$  = 4.6 Hz, CH<sub>3</sub>NH), 2.24 (t,  $J$  = 2.6 Hz, C3-H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 158.84 (C=O), 79.53 (C2), 71.84 (C3), 37.83 (C1), 33.69 (CONCH<sub>3</sub>), 27.67 (CH<sub>3</sub>NH). Anal. (C<sub>8</sub>H<sub>10</sub>N<sub>2</sub>O) 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<sub>2</sub>, ether); IR (KBr disk) 3220, 2100, 1630, 1500 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.94 (d,  $J$  = 2.4 Hz, 2 CH<sub>2</sub>), 2.92 (s, 2 CH<sub>3</sub>), 2.26 (t,  $J$  = 2.4 Hz, 2 C≡CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 163.65 (C=O), 79.37 (2 C≡CH), 72.24 (2 C≡CH), 40.03 (2 CH<sub>2</sub>), 36.16 (2 CH<sub>3</sub>). Anal. (C<sub>9</sub>H<sub>12</sub>N<sub>2</sub>O) 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<sub>4</sub>NBr (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<sup>23</sup> (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<sub>2</sub>, ether-methanol (5%)]; IR (KBr disk) 3375, 3220, 2100, 1620, 1540 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 5.35 (qd,  $J$  = 7.1 and 2.4 Hz, C1-H), 4.95 (br, NH), 2.86 (s, CONCH<sub>3</sub>), 2.80 (d,  $J$  = 4.6 Hz, CH<sub>3</sub>NH), 2.29 (d,  $J$  = 2.4 Hz, C3-H), 1.32 (d, C1-CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 158.04 (C=O), 83.30 (C2), 71.13 (C3), 42.07 (C1), 28.58 (CON-CH<sub>3</sub>), 27.46 (CH<sub>3</sub>NH), 19.74 (C1-CH<sub>3</sub>). Anal. (C<sub>7</sub>H<sub>12</sub>N<sub>2</sub>O) 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<sup>56</sup> (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<sub>2</sub>, ether-light petroleum (1:1)]; IR (neat liquid) 3265, 2120, 1820, 1805 (shoulder), 1740 (br) cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 4.30 (s, ring CH<sub>2</sub>), 4.26 (d,  $J$  = 2.6 Hz, C1-H's), 2.65 (t,  $J$  = 2.6 Hz, C3-H), 1.54 [s, C(CH<sub>3</sub>)<sub>3</sub>]; <sup>13</sup>C NMR (CD<sub>3</sub>OD)<sup>57</sup> δ 168.53 (CH<sub>2</sub>C=O), 152.94 and 149.57 (C=O's), 84.93 (C=O), 77.58 (C2), 73.01 (C3), 49.97 (ring CH<sub>2</sub>), 28.57 (C1), 28.17 [C(CH<sub>3</sub>)<sub>3</sub>]. Anal. (C<sub>11</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>) 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<sub>2</sub>, ether); IR (KBr disk) 3265, 2115, 1770, 1690 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.08 (d,  $J$  = 2.6 Hz, C1-H's), 3.93–3.70 and 3.58–3.33 (m's, ring CH<sub>2</sub>'s), 2.25 (t,  $J$  = 2.4 Hz, C3-H), 1.53 [s, C(CH<sub>3</sub>)<sub>3</sub>]; <sup>13</sup>C NMR (CDCl<sub>3</sub>) 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<sub>2</sub>'s), 32.99 (C1), 27.80 [C(CH<sub>3</sub>)<sub>3</sub>]. Anal. (C<sub>11</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>) 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<sub>2</sub>, ether); IR (KBr disk) 3250, 2110, 1725, 1700 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.95 (qd,  $J$  = 7.1 and 2.2 Hz), 3.94–3.21 (m, ring CH<sub>2</sub>'s), 2.32 (d,  $J$  = 2.4 Hz, C3-H), 1.53 [s, C(CH<sub>3</sub>)<sub>3</sub>], 1.39 (d,  $J$  = 7.2 Hz, C1-CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 152.88 and 150.35 (C=O's), 81.91 (C=O), 81.05 (C2), 72.06 (C3), 40.31 (ring CH<sub>2</sub>'), 39.66 (C1), 36.26 (ring CH<sub>2</sub>'), 27.77 [C(CH<sub>3</sub>)<sub>3</sub>], 19.12 (C1-CH<sub>3</sub>). Anal. (C<sub>12</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>) C, H, N.

**1-Formyl-2-imidazolidone (52).** This compound was prepared according to a literature procedure<sup>39</sup> in 72% yield: mp 155–157 °C (lit. mp 151–152 °C,<sup>39a</sup> 156–158 °C,<sup>39b</sup>); <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 8.82 (s, HC=O), 3.96–3.41 (m's, CH<sub>2</sub>'s); <sup>13</sup>C NMR (CD<sub>3</sub>OD) δ 161.79 (HC=O), 158.60 (NCON), 40.27 and 38.62 (CH<sub>2</sub>'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<sub>2</sub>, ether); IR (neat liquid) 3255, 2120, 1735 (ring C=O),<sup>58</sup> 1690 (HC=O)<sup>58</sup> cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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 <sup>13</sup>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 <sup>13</sup>C NMR spectrum taken in CDCl<sub>3</sub>, 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<sub>2</sub>'s), 2.43 (t,  $J = 2.4$  Hz, C3-H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 159.74 (HC=O), 154.02 (NCON), 76.29 (C2), 73.26 (C3), 40.87 and 36.67 (ring CH<sub>2</sub>'s), 32.47 (C1). Anal. (C<sub>7</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>) H, N; C: calcd, 55.26; found, 54.78.

**N,1-Dimethyl-4-(1-pyrrolidinyl)-2-butynylamine (57).** A mixture of trifluoroacetamide derivative 55<sup>21</sup> (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<sub>2</sub>CO<sub>3</sub>), 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<sup>-1</sup>; <sup>1</sup>H NMR (fumarate, CD<sub>3</sub>OD) 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<sub>3</sub>NH), 2.15–1.91 (m, pyrrolidine β-H's), 1.57 (d,  $J = 6.8$  Hz, C1-CH<sub>3</sub>); <sup>13</sup>C NMR (fumarate, CD<sub>3</sub>OD) 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<sub>3</sub>NH), 24.46 (pyrrolidine β-C's), 18.62 (C1-CH<sub>3</sub>). Anal. (C<sub>10</sub>H<sub>13</sub>N<sub>2</sub>·1.5C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) 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<sub>4</sub>OH as the eluent. The reaction mixture was alkalized by addition of 10% aqueous K<sub>2</sub>CO<sub>3</sub> solution (50 mL) under external cooling (ice bath) and was extracted with dichloromethane (4 × 125 mL). The combined organic layers were dried (K<sub>2</sub>CO<sub>3</sub>), 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<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 5.26 (m, C1-H), 4.78 (br, NH<sub>2</sub>), 3.40 (d,  $J = 2.0$  Hz, C4-H's), 2.89 (s, NCH<sub>3</sub>), 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<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>) 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<sub>3</sub>), 23.45 (pyrrolidine β-C's), 19.96 (C1-CH<sub>3</sub>). Anal. (C<sub>11</sub>H<sub>19</sub>N<sub>3</sub>O) 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)<sup>3</sup> (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<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 5.02 (br, NH<sub>2</sub>), 4.10 (t,  $J = 2.0$  Hz, C1-H's), 3.40 (t,  $J = 2.0$  Hz, C4-H's), 2.96 (s, CH<sub>3</sub>), 2.75–2.42 (m, pyrrolidine α-H's), 1.91–1.68 (m, pyrrolidine β-H's); <sup>13</sup>C NMR (CDCl<sub>3</sub>) 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<sub>3</sub>), 23.39 (pyrrolidine β-C's). Anal. (C<sub>10</sub>H<sub>17</sub>N<sub>3</sub>O) C, H, N.

**General Procedure for Synthesis of 33, 34, 40, 48 and of Test Compounds 17, 18, 20, 22, and 23.**<sup>59</sup> 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-dioximidazolidin-3-yl]hexadiene (41).<sup>60</sup> 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<sub>2</sub>, chloroform-methanol (10%)]; IR (KBr disk) 1805, 1725 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.32 (t,  $J = 2.0$  Hz, C1-H's), 4.24 (ring CH<sub>2</sub>C=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<sub>3</sub>)<sub>3</sub>]; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 166.49 (CH<sub>2</sub>C=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<sub>2</sub>C=O), 43.21 (C4), 28.51 (C1), 27.98 [C(CH<sub>3</sub>)<sub>3</sub>], 23.72 (pyrrolidine β-C's). Anal. (C<sub>16</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub>) 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<sub>2</sub>, ether); IR (KBr disk) 1815, 1740 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.35 (s, 2 CH<sub>2</sub>),<sup>61</sup> 4.26 (s, 2 ring CH<sub>2</sub>),<sup>61</sup> 1.56 [s, 2 C(CH<sub>3</sub>)<sub>3</sub>]; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 166.16 (2 ring CH<sub>2</sub>C=O), 150.60 and 148.06 (C=O's), 84.60 (2 C—O), 71.29 (2 C),<sup>62</sup> 67.55 (2 C3),<sup>62</sup> 48.74 (2 ring CH<sub>2</sub>), 28.51 (2 C1), 27.83 [2 C(CH<sub>3</sub>)<sub>3</sub>]. Anal. (C<sub>22</sub>H<sub>26</sub>N<sub>4</sub>O<sub>8</sub>) C, H, N.

**General Procedure for N-Deprotection of *t*-Boc Derivatives 33, 34, 40, 41, and 48.**<sup>59</sup> 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 alkalized by addition of aqueous 10% K<sub>2</sub>CO<sub>3</sub> (175 mL) and was then extracted with dichloromethane (4 × 175 mL). The combined organic layers were dried (K<sub>2</sub>CO<sub>3</sub>), 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<sup>-1</sup>; <sup>1</sup>H NMR (oxalate, D<sub>2</sub>O) δ 4.22 (t,  $J = 2.2$  Hz, 2 H), 3.95 (s, ring CH<sub>2</sub>C=O), 3.92 (t, partially obscured,  $J = 1.7$  Hz, 2 H), 3.15 (s, 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); <sup>13</sup>C NMR (oxalate, D<sub>2</sub>O) δ 175.29 (CH<sub>2</sub>C=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<sub>2</sub>C=O), 44.78 (C4), 29.09 (C1), 24.52 (pyrrolidine β-C's).

**1,6-Bis(2,4-dioximidazolidin-3-yl)hexadiene (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%)<sup>62</sup> of 42; mp 212–214 °C; IR (KBr disk) 3250, 1780, 1720 (br) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.21 (s, 2 NH), 4.27 (s, 2 ring CH<sub>2</sub>), 3.96 (s, 2 CH<sub>2</sub>); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 170.92 (2 CH<sub>2</sub>C=O), 155.98 (2 NCON), 73.74 (2 C2), 65.72 (2 C3), 45.95 (2 CH<sub>2</sub>C=O), 27.35 (2 C1). Anal. (C<sub>12</sub>H<sub>10</sub>N<sub>4</sub>O<sub>4</sub>·0.25H<sub>2</sub>O) 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.<sup>63</sup> The Tyrode's solution contained hexamethonium (0.3 mM). Ileal contractions were recorded isotonicly 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 (<sup>1</sup>H 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.<sup>64</sup> 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).<sup>63</sup> 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  $\mu$ M (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.<sup>63</sup>

**Muscarinic Receptor Binding Assay.** Binding assays were performed using the filtration method described by Yamamura and Snyder.<sup>65</sup> 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 [<sup>3</sup>H]-3-quinuclidinyl benzilate ([<sup>3</sup>H]QNB; 43 Ci/mmol; New England Nuclear; 0.003–1.0 nM) with the cortical homogenate (0.1 mL; 30–60  $\mu$ g 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 [<sup>3</sup>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  $\mu$ M 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 [<sup>3</sup>H]QNB binding by 50%) were also obtained by fitting the data to a one-site binding model by nonlinear regression analysis.<sup>66</sup> The  $IC_{50}$  values were corrected

for receptor occupancy by [<sup>3</sup>H]QNB as described by Cheng and Prusoff<sup>67</sup> to give  $K_i$  values (concentration of ligand that causes half-maximal receptor occupancy in the absence of [<sup>3</sup>H]QNB). Protein was determined by the method of Lowry et al.<sup>68</sup> using albumin as the standard. Saturation studies showed that [<sup>3</sup>H]-QNB has a  $K_D = 0.18 \pm 0.03$  nM and a  $B_{max} = 478 \pm 50$  fmol/mg protein ( $N = 4$ ).

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**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:** <sup>1</sup>H NMR spectral data for 15–23, 33, 34, 46–48, 50, and 51, <sup>13</sup>C NMR spectral data for 15–23, 27 (in CD<sub>3</sub>OD), 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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