2-Ethynylbenzenealkanamines. A New Class of Calcium Entry Blockers

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A series of 2-(aryl- or alkylethynyl)benzenealkanamines were synthesized. They exhibit antihypertensive activity in spontaneously hypertensive rats and coronary vasodilator activity with minimal negative inotropic activity in the "Langendorff" guinea pig heart in vitro. They have been shown to exert their activity by inhibition of Ca^{2+} influx across cell membranes. Optimal activity is found among the *N*-(arylethyl)-5-methoxy-α-methyl-2-(phenylethynyl)benzeneethanamines and -propanamines.

Calcium entry blockers continue to enjoy an ever increasing role in cardiovascular medicine.[1] Structurally, these agents can be divided into two main groups, the dihydropyridines, such as nifedipine, nisoldipine, nitrendipine, and related compounds, and the calcium entry blockers with basic side chains including verapamil, diltiazem, bepridil, flunarizine, lidoflazine, and prenylamine. While structure–activity relationships among the dihydropyridines are well known,[2] there is no single well-accepted pharmacophore for the calcium entry blockers with basic side chains. They constitute a diverse group of structures. A number of attempts have been made to classify calcium entry blockers into groups based on biological properties.[3] These attempts have not, however, clarified the structural relationships among the basic calcium entry blockers. The emergence of new structural types of basic calcium entry blockers would be of value in formulating a pharmacophore for these agents.

The major side effects of the dihydropyridine class are different from the major side effects of diltiazem, verapamil, and other basic calcium entry blockers.[4] Exacerbation of angina resulting from reflex tachycardia has proven to be a problem with dihydropyridines,[5] while abnormalities of AV nodal conduction have been a problem with basic calcium entry blockers.[4] In animals, negative inotropic activity is a feature common to both dihydropyridines and basic calcium entry blockers.[6] Negative inotropic activity could play a role in limiting the maximum doses employable and, consequently, the ultimate efficacy of currently used agents.

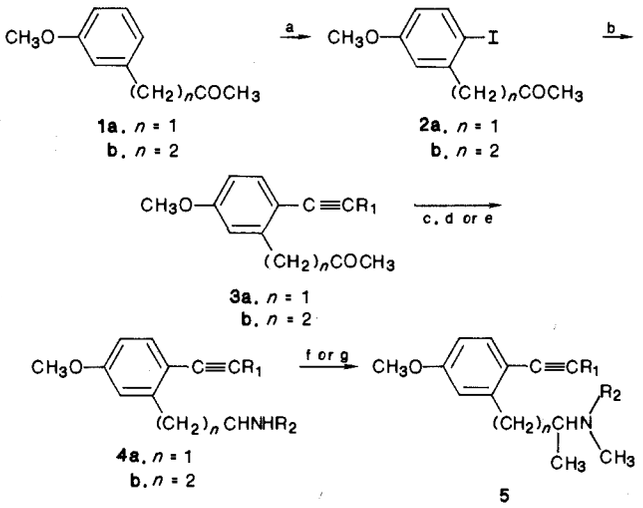
In order for a new calcium entry blocker to gain acceptance, it would need to possess greater efficacy and/or fewer side effects than currently used agents.

We report here the synthesis and biological testing of 2-ethynylbenzenealkanamines (**4**, **5**, and **12**), a new class of basic calcium entry blockers that have a limited component of negative inotropic activity. Certain of these compounds do not cause reflex tachycardia.

Chemistry. The 2-ethynylbenzenealkanamines were prepared according to the sequences of Scheme I–III and the compounds prepared are shown in Tables I and II.

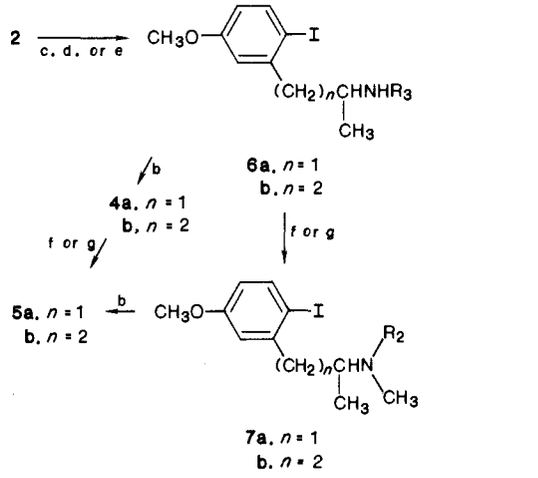
The (methoxyphenyl)alkanones, **1**, were prepared by literature methods.[7,8] Iodinations of arylalkanones were carried out with iodine and silver acetate[9] to give **2**.

Scheme I[a]



[a] Procedures: (a) I_2, AgOAc, (b) $R_1C{\equiv}CH$, $(Ph_3P)_4Pd(0)$, CuI, Et_3N. (c) R_2NH_2, $NaBH_3CH$. (d) 5A molecular sieves, R_2NH_2, $NaBH_4$. (e) $PhCH_3$, TsOH, R_2NH_2, $NaBH_3CN$. (f) $PhCH_3$, TsOH, R_2NH_2, $NaBH_4$. (g) $NaBH_4$, CH_2O. (h) $NaBH_3CN$. (i) $NaBH_4$.

Scheme II[a]



[a] Procedures: (b) $R_1C{\equiv}CH$, $(Ph_3P)_4Pd(0)$, CuI, Et_3N. (c) R_2NH_2, $NaBH_3CN$. (d) 5A molecular sieves, R_2NH_2, $NaBH_4$. (e) $PhCH_3$, TsOH, R_2NH_2. (f) $PhCH_3$, TsOH, R_2NH_2, $NaBH_4$. (g) $NaBH_4$, CH_2O.

Schemes I and II differ, primarily, in the sequence in which the reactions were performed. According to Schemes I and II, iodine was replaced from the aromatic rings by substituted acetylenes through the use of $(Ph_3P)_4Pd(0)$ as catalyst[10] to give **3**. Reductive aminations

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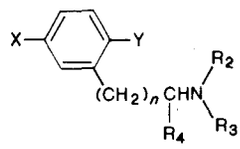
Table I. Benzenealkaneamines

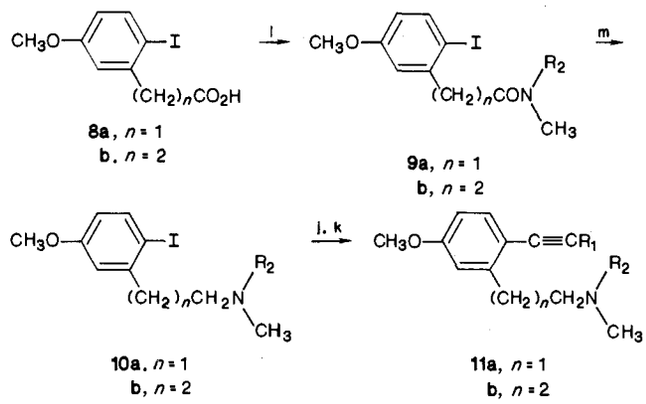


6: R_3 = H, R_4 = CH_3, Y = I, X = CH_3O **12**: R_3 = H, R_4 = CH_3, Y = H, X = CH_3O
7: R_3 = CH_3, R_4 = CH_3, Y = I, X = CH_3O **15**: R_3 = H, R_4 = CH_3, Y = Br, X = F
10: R_3 = CH_3, R_4 = H, Y = I, X = CH_3O **16**: R_3 = CH_3, R_4 = CH_2, Y = Br, X = F

no.	n	R_2	Scheme	procedures[a]	% yield	recryst solvent	mp, °C	formula[b,c]	anal.
6g	2	$(CH_2)_2$-3,5-$(CH_3O)_2C_6H_3$	II	c	69	MeOH	143–145	$C_{21}H_{28}INO_3$·HCl	CHN
6h	1	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$	II	e	95	EtOH	170–172	$C_{20}H_{26}INO_3$·HCl	CHN
6i	1	$(CH_2)_2$-2,3-$(CH_3O)_2C_6H_3$	II	c	51	EtOH	202–205	$C_{18}H_{20}Cl_2IO$·$C_2H_2O_4$	CHN
7h	1	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$	II	h	95	EtOH	178–179	$C_{21}H_{28}INO_3$·$C_2H_2O_4$	CHN
7j	1	$(CH_2)_2Ph$	II[d]	e, h	55	MeOH/PrOH	165–168	$C_{19}H_{24}INO$·$C_2H_2O_4$	CHN
7v	1	$(CH_2)_4Ph$	II[d]	e, h	30	MeOH/2PrOH	131–135	$C_{21}H_{28}INO$·$C_2H_2O_4$	CHN
7w	1	$(CH_2)_3Ph$	II[d]	e, h	36	2-PrOH/Et_2O	172–173	$C_{20}H_{26}INO$·HCl	CHN
10a	1	CH_3	III	m	75	2-PrOH	168–170	$C_{11}H_{16}INO$·HCl	CH
10b	2	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$	III	m	39	EtOH/Et_2O	105–106	$C_{21}H_{28}INO_3$·$C_7H_8SO_3$	CHN
10f	1	CH_3	III	m	84		164–166	$C_{12}H_{18}INO$·HCl	CH
12	1	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$		d	72	MeOH	131–133	$C_{20}H_{27}NO_3$·HCl	CHN
15	2	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$		c	98	EtOH	188–190	$C_{20}H_{25}BrFNO_2$·HCl	CHN
16	2	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$		h	66	MeOH	173–174	$C_{21}H_{27}BrFNO_2$·$C_2H_2O_4$	CHN

[a] See the lettered reagents following Scheme III. [b] $C_2H_2O_4$ is ethanediolate. [c] $C_7H_8SO_3$ is 4-methylbenzenesulfonate. [d] The intermediate **6** was not isolated, but was methylated in situ to give **7**.

Scheme III[a]



[a] Procedures: (j) $R_1C{\equiv}CCu$, pyridine. (k) $R_1C{\equiv}CH$, *n*-BuLi, $ZnCl_2$, $(Ph_3P)_4Pd(0)$. (l) ClCOCOCl, CH_3NHR_2. (m) BH_3.

of ketones (Scheme I, **3** to **4**; Scheme II, **2** to **6**) were carried out by several procedures (procedures b–f, Scheme III).[11] Compound **12** was prepared from **1a** (procedure d, Scheme III).

Reductive methylations (**4** to **5**, **6** to **7**) were performed with formaldehyde and either $NaBH_4$ or $NaBH_3CN$ as the reducing agent. Compound **13** was prepared from **4b** by reductive alkylation using butyraldehyde and sodium borohydride.

Scheme III differs from the other schemes in that the amine functionality was elaborated by amide formation and subsequent borane reduction. Iodinations of the alkanoic acids (**8**) were performed with ICl. Attachment of the acetylene to the aryl ring was brought about either by palladium-catalyzed coupling of the zinc acetylide to the aryl halide[12] or by cuprous acetylide coupling to the aryl halide.[13]

Compounds **17** and **20**, the assemblies of which are not controlled by an electron-donating substituent, were prepared from 4-(2-bromo-5-fluorophenyl)-2-butanone (**14**) and 1-(2-bromophenyl)-2-propanone (**18**),[14] respectively. Ketone **14** was prepared by the route of Boatman, Harris, and Hauser.[15] Compound **17** was elaborated by a route analogous to Scheme II using bromo intermediates instead of iodo. Compound **20** was prepared by a route analogous to Scheme I.

Biological Activity. The compounds were evaluated for their ability to lower blood pressure in the spontaneously hypertensive rat (SHR).[16] Maximum fall in blood pressure (mmHg) following the indicated oral dose is shown in Table III.

The ability of the compounds to effect an increase in coronary blood flow was studied with the "Langendorff", guinea pig heart in vitro.[17] The quantity C_{175} tabulated (Table III) refers to the concentration of drug (micromolar) needed to elicit a 75% increase beyond control in coronary flow. The quantity Ei refers to negative inotropic activity (percent of control contractility) at the concentration of drug needed to achieve a 75% increase in coronary flow.

As can be seen from Table III, the 2-ethynylbenzenealkanamines, in general, decrease blood pressure in the SHR and increase coronary flow in the Langendorff heart. In addition, many of the compounds lack a pronounced negative inotropic effect, and a balance of these three factors was used to determine our interest in specific compounds. Potency in lowering blood pressure, within structurally similar subgroups of compounds, parallels potency in increasing coronary flow.

Selected compounds have also been evaluated for their ability to inhibit ^{45}Ca uptake and development of isometric tension in rabbit aorta (vascular smooth muscle) in vitro.[18] The results are shown in Table IV. The compounds tested all inhibited Ca^{2+} influx in response to a stimulus of KCl as did the reference compounds diltiazem and verapamil.

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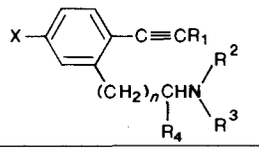
Table II. 2-Ethynylbenzenealkaneamines



4: R_3 = H, R_4 = CH_3, X = CH_3O **13**: R_3 = n-C_4H_9, R_4 = CH_3, X = CH_3O
5: R_3 = CH_3, R_4 = CH_3, X = CH_3O **17**: R_3 = CH_3, R_4 = CH_3, X = F
11: R_3 = CH_3, R_4 = H, X = CH_3O **20**: R_3 = CH_3, R_4 = CH_3, X = H

no.	n	R_1	R_2	method of scheme	procedures[a]	% yield	recryst solvent	mp, °C	formula[b-d]	anal.
4a	1	Ph	$(CH_2)_2$-3,5-$(CH_3O)_2C_6H_3$	I	c	56	MeOH	186–188	$C_{28}H_{31}NO_3 \cdot 0.5C_4H_4O_4 \cdot 0.25H_2O$	CHN
4b	2	Ph	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$	I	e	40	CH_3CN/Et_2O	128–130	$C_{29}H_{33}NO_3 \cdot HCl$	CHN
4c	1	Ph	$(CH_2)_2$-3-$CH_3OC_6H_4$	I	c	35	EtOH	152–154	$C_{27}H_{29}NO_2 \cdot 0.5C_4H_4O_4$	CHN
4d	1	Ph	$(CH_2)_2$-1-naphthyl	I	b	73	$CHCl_3$	107–110	$C_{30}H_{29}NO \cdot HCl \cdot 0.33H_2O$	CHN·H_2O
4e	1	Ph	$(CH_2)_2$-3-ClC_6H_4	I	b	40	EtOH	178–179	$C_{26}H_{26}ClNO \cdot HCl$	CHN
4f	1	Ph	$(CH_2)_2$-3,4-$Cl_2C_6H_3$	I	c	51	$MeOH/CH_3CN$	189–191	$C_{26}H_{25}Cl_2NO \cdot HCl$	CHN
4g	2	Ph	$(CH_2)_2$-3,5-$(CH_3O)_2C_6H_3$	II	a	69	CH_3CN/EtOH	144–146	$C_{29}H_{33}NO_3 \cdot HCl$	CHN
4h	1	Ph	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$	II	j	45	EtOH	165–167	$C_{28}H_{31}NO_3 \cdot 0.5C_4H_4O_4 \cdot 0.33H_2O$	CHN
4i	1	Ph	$(CH_2)_2$-2,3-$Cl_2C_6H_3$	II	a	29		163–165	$C_{26}H_{25}Cl_2NO \cdot HCl$	CHN
4j	1	Ph	$(CH_2)_2$-4-$NO_2C_6H_4$	I	b	66	EtOH	155–157	$C_{26}H_{26}N_2O_3 \cdot 0.5C_4H_4O_4$	CHN
4k	1	Ph	$(CH_2)_2$-4-ClC_6H_4	I	b	50	2-PrOH	165–167	$C_{26}H_{26}ClNO \cdot 0.5C_4H_4O_4 \cdot 0.10H_2O$	CHN·H_2O
5a	1	Ph	$(CH_2)_2$-3,5-$(CH_3O)_2C_6H_3$	I	g	51	2-PrOH	165–166	$C_{29}H_{33}NO_3 \cdot HCl \cdot {}^1/_{16}H_2O$	CHN·H_2O
5b[e]	2	Ph	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$	I	f	88	2-PrOH	116–120	$C_{30}H_{35}NO_3 \cdot HCl$	CHN
5c	1	Ph	$(CH_2)_2$-3-$CH_3OC_6H_4$	I	f	62	2-PrOH	150–151	$C_{28}H_{31}NO_2 \cdot HCl$	CHN
5d	1	Ph	$(CH_2)_2$-1-naphthyl	I	g	60	2-PrOH	168–171	$C_{31}H_{31}NO \cdot HCl \cdot 0.13H_2O$	CHN·H_2O
5e[e]	1	Ph	$(CH_2)_2$-3-ClC_6H_4	I	g	64	$EtOH/Et_2O$	83–88	$C_{27}H_{28}ClNO \cdot HCl \cdot 0.5H_2O$	CH·H_2O
5f	1	Ph	$(CH_2)_2$-3,4-$Cl_2C_6H_3$	I	g	90	2-PrOH	124–127	$C_{27}H_{27}Cl_2NO \cdot C_4H_4O_4$	CHN
5g	2	Ph	$(CH_2)_2$-3,5-$(CH_3O)_2C_6H_3$	II	f	92	EtOH	127–129	$C_{30}H_{35}NO_3 \cdot C_4H_4O_4$	CHN
5h[e]	1	Ph	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$	II	g	62	2-PrOH	124–126	$C_{29}H_{33}NO_3 \cdot C_4H_4O_4$	CHN
5i	1	Ph	$(CH_2)_2$-2,3-$Cl_2C_6H_3$	II	f	47	CH_3CN	153–155	$C_{27}H_{27}Cl_2NO \cdot HCl$	CHN
5l	1	Ph	$(CH_2)_2Ph$	II	a	54	$2\text{-PrOH}/CH_3CN$	150–151	$C_{27}H_{29}NO \cdot HCl$	CHN
5m	1	4-ClC_6H_4	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$	II	a	35	EtOH	140–141	$C_{29}H_{32}ClNO \cdot 0.5C_4H_4O_4$	CHN
5n	1	4-$CF_3C_6H_4$	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$	II	a	33	2-PrOH	117–119	$C_{30}H_{32}F_3NO_3 \cdot 0.5C_4H_4O_4$	CHN
5o	1	4-NCC_6H_4	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$	II	a	27	2-PrOH/EtOH	130–132	$C_{30}H_{32}N_2O_3 \cdot 0.5C_4H_4O_4$	CHN
5p	1	4-$CH_3SC_6H_4$	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$	II	a	30	2-PrOH	93–95	$C_{30}H_{35}NO_3S \cdot HCl$	CHN
5q	1	4-CH_3SOC_6H4	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$	II	a	42	MeOH/2-PrOH	199–201	$C_{30}H_{35}NO_4S \cdot HCl$	CHN
5r	1	4-$(CH_3)_2NC_6H_4$	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$	II	a	17	MeOH/2-PrOH	99–100	$C_{31}H_{38}N_2O_3$	CHN
5s	1	4-FC_6H_4	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$	II	a	83	2-PrOH	132–134	$C_{29}H_{32}FNO_3 \cdot C_4H_4O_4$	CHN
5t	1	4-$(CH_3)_2CHC_6H_4$	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$	II	a	6	hexane	55–68	$C_{32}H_{39}NO_3$	CHN
5u	1	Ph	CH_2-3,4-$(CH_3O)_2C_6H_3$	I[f]	e, h	28[i]	MeOH/2-PrOH	180–182	$C_{28}H_{31}NO_3 \cdot HCl \cdot 0.15H_2O$	CHN
5v	1	Ph	$(CH_2)_4Ph$	II	a	58	$2\text{-PrOH}/Et_2O$	133–135	$C_{29}H_{33}NO \cdot HCl$	CHN
5w	1	Ph	$(CH_2)_3Ph$	II	a	67	$MeOH/Et_2O$	204–205	$C_{26}H_{31}NO \cdot HCl$	CHN
5x	1	Ph	n-C_6H_{13}	I[f]	b, f	64	EtOAc	97–99	$C_{25}H_{33}NO \cdot C_4H_4O_4$	CHN
11a	1	Ph	CH_3	III	i	44	EtOH	190–191	$C_{19}H_{21}NO \cdot HCl$	CH
11b	2	Ph	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$	III	j	56	t-BuOH/Et_2O	122–129	$C_{29}H_{33}NO_3 \cdot HCl$	CHN
11c	2	C_2H_5	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$	III	j	15	2-PrOH	114–117	$C_{25}H_{33}NO_3 \cdot 2C_6H_{13}NSO_3$	CHN
11d	2	$(CH_2)_2Ph$	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$	III	j	19	*h*	oil	$C_{31}H_{37}NO_3$	CHN
11e	2	n-C_4H_9	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$	III	j	13	2-PrOH	107–110	$C_{27}H_{34}NO_3 \cdot 2C_6H_{13}NSO_3$	CNHS·H_2O
11f	2	Ph	CH_3	III	i	30	EtOH	128–129	$C_{20}H_{23}NO \cdot C_4H_4O_4$	CHN
13	1	Ph	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$		$NaBH_3CN$ n-C_3H_7CHO	43	*h*	oil	$C_{32}H_{38}NO_3$	CHN[g]
17	2	Ph	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$		a	29	EtOAc	124–126	$C_{29}H_{32}FNO_2 \cdot HCl \cdot 0.2H_2O$	CHN·H_2O
20	1	Ph	$(CH_2)_2$-3,4-$(CH_3O)_2C_6H_3$		b, g	15	*h*	oil	$C_{28}H_{31}NO_3$	CHN

[a] See the lettered reagents following Scheme III. [b] $C_4H_4O_4$ is (*E*)-2-butenedioate. [c] $C_2H_2O_4$ is ethanedioate. [d] $C_6H_{13}NSO_3$ is cyclohexylsulfamate. [e] Via 4. [f] N-Methylated without isolation of 4. [g] Anal. Calcd for $C_{32}H_{39}NO_3$: C, 79.14; H, 8.09; N, 2.88. Found: C, 78.63; H, 8.16; N, 2.81; exact mass MS (M + 1) calcd 486.30082, found 486.30354. [h] Flash chromatographed on SiO_2. [i] Overall yield.

Table III. Biological Activities

	"Langendorff" heart			SHR		
no.	C_{175},[a] μM	Ei (% control)	P (Ei)	max fall Bp, mmHg	dose, mg/kg po	P
4a	7.5×10^{-4}	120	0.026	36	10	<0.05
4b	0.07	123	$0.001 < P < 0.004$	20	30	<0.005
4c	0.004	115	$0.019 < P < 0.027$	56	10	<0.005
4d	0.083	77	$0.003 < P < 0.079$	48	30	<0.005
4e	0.03	85	$0.007 < P < 0.08$	52	3	<0.01
4f	0.006	115	>0.205	43	3	<0.005
4g	2.1	87	$0.045 < P < 0.5$	34	30	<0.001
4h	0.027	95	>0.5	37	3	<0.001
4i	0.0048	83	$0.031 < P < 0.093$	45	3	<0.005
4j	>3.0	>66	<0.05	66	30	<0.001
4k	>3.0	>25	<0.05	39	10	<0.01
5a	0.0025	100	$0.50 < P < 0.075$	66	3	<0.001
5b	0.025	135	$0.055 < P < 0.06$	40	30	<0.001
5c	0.0035	95	$0.21 < P < 0.73$	67	3	<0.01
5d	0.19	61	$0.005 < P < 0.035$	43	3	<0.005
5e	0.005	95	$0.53 < P < 0.58$	64	3	<0.005
5f	0.004	90	>0.5	67	1	<0.001
5g	0.095	105	$0.15 < P > 0.76$	42	30	$<1 \times 10^{-4}$
5h	0.025	70	<0.05	53	1	<0.001
5i	0.015	58	$0.007 < P < 0.034$	111	3	$<1 \times 10^{-4}$
5l	0.5	115	>0.5	43	10	<0.01
5m	0.3	85	>0.5	46	30	<0.001
5n	2.0	90	>0.5	49	30	<0.02
5o	0.45	75	<0.05	27	10	<0.04
5p	0.55	80	0.5	45	30	<0.001
5q	3.0	10	<0.001	29	29	NS
5r	0.035	115	$0.009 < P < 0.31$	69	3	<0.001
5s	0.0013	78	$0.003 < P < 0.089$	43	3	$<1 \times 10^{-4}$
5t	4.04	34	<0.001	13	3	NS
5u	3.0	50	<0.05	20	10	<0.002
5v	2.75	90	>0.05	74	30	<0.01
5w	2.5	95	>0.5	52	30	<0.01
5x	>3.0			48	10	<0.001
11a	3.0	90	>0.05	18	30	<0.01
11b	3.0	85	<0.05	62	100	<0.01
11c	1.0	80	<0.05	24	10	<0.01
11d	1.25	100	>0.5	12	10	<0.001
11e	0.2	100	>0.5	35	100	<0.01
11f	0.3	110	>0.5	22	30	NS
12	>10			18	30	<0.026
13	>3			49	30	>0.001
17	0.34	85	0.45	50	30	<0.01
20	0.2	90	>0.05	13	10	NS
nifedipine	0.013	85	$0.014 < P < 0.06$	52	10	<0.01
verapamil	0.10	35	<0.001	67	30	<0.001
diltiazem	0.18	90	>0.05	48	30	$<1 \times 10^{-4}$

[a] In all cases where a C_{175} could be determined, the increase in coronary outflow (to 175% of control flow) was highly significant.

Table IV. Calcium Flux and Tension

	isomeric tension: % change from control		calcium influx: % change from control	
compound (10 μM)	KCl (60 μM)	NE (10 μM)	KCl (60 μM)	NE (10 μM)
4a	−15	−13	−42*	−23*
4f	−20*[a]	−5	−21*	−23
4h	−68*	−45*	−46*	−27*
5a	−68*	−22*	−41*	−10
5b	−71*	−47*	−42*	−34*
diltiazem	−84*	−8	−18*	−37*
verapamil	−89*	−18	−30*	−22

[a] (*) significant, $p < 0.05$.

Compounds **4a**, **4h**, and **5b** inhibited Ca^{2+} influx in response to a stimulus of norepenephrine (NE) as did diltiazem. The test and reference compounds with the exception of **4a** inhibited the development of isometric tension in response to KCl while only compounds **4h**, **5a**, and **5b** inhibited development of tension in response to NE.

Thus, while differences in profile exist, it is likely that calcium entry blockade is the mechanism of action of the vasodilation observed with these drugs.

Structure–Activity Relationships. Structural features that contribute to maximum potency are as follows: the 5-methoxy group was more effective in increasing vasodilatory potency than the corresponding fluoro or hydrogen substituents (e.g., **5b** and **5h** vs. **17** and **20**, respectively). The compounds with two carbon atoms connecting the aromatic ring and the amine nitrogen ($n = 1$) tend to be more potent as antihypertensives than the compounds with a three-carbon linkage ($n = 2$) (**5h** vs. **5b**).

The group R_1 can encompass a range of lipophilic functions such as ethyl (**11c**), phenethyl (**11d**), and butyl (**11e**) with retention of vasodilator activity. It is unlikely, therefore, that this grouping plays a key role in binding. An unsubstituted phenyl is the optimum substituent on the acetylene (R_1). Substituents on phenyl other than fluoro or dimethylamino reduced activity (**5m–q**,t vs. **5h**). When R_1 is alkyl rather than aryl, the compounds tend to be more effective as vasodilators than as antihypertensives (**11e** vs. **11b**). Compound **12** which lacks the alkynyl function, has little antihypertensive or vasodilator activity.

For maximum vasodilator and antihypertensive potency, a group R_2 of substantial size on nitrogen is needed. Ar-

alkyl groups and in particular phenethyl groups confer excellent potency (**4**, **5a–k**). The substituents on the phenyl ring of the phenethyl group exert a powerful effect on potency. A single chloro or nitro group (**4k**, **4j**) in the para position abolishes vasodilator activity while substituents at the meta position and multiple substituents enhance activity (e.g., **4c**, **4a**). An *n*-hexyl group as R_2 resulted in a compound (**5x**) with antihypertensive activity but no vasodilator activity. The activity shown by compounds of type **4** is similar to the analogous compounds of type **5**. The secondary amines of type **4** are likely to have the greater vasodilator component while the tertiary *N*-methylamines of type **5** the greater antihypertensive component (**4a** vs. **5a**). Compounds of type **11** are, in general, less potent in respect to both blood pressure and vasodilation.

Regression analyses on vasodilator data was carried out on three groups of compounds. The parameters[19] examined were π (hydrophobic substituent constants), MR (molar refractivity, bulk), σ (Hammett constants), and their squared terms, π^2, MR^2, and σ^2. Compounds of type **5**, $n = 1$, R_1 = Ph were selected as the first group for QSAR analysis. Eight variations of substituents on the phenethyl phenyl (R_2) were examined. A fit was obtained for the equation: $\log (1/C_{175}) = -0.74 + 0.58(MR) - 0.027(MR)^2$; $n = 8$, $F = 8.5$, $r^2 = 0.77$, $s = 0.48$. Where n is the number of compounds used to derive the equation, F is the Fischer statistic, r^2 is the squared correlation coefficient, and s is the standard deviation. The optimum activity is predicted at MR = 10.9, close to the value for the dichloro-substituted phenyl ring. Thus, low bulk substituents, F and H, are needed to move away from the function's minimum activity near MR = 10.

A second group of nine compounds of type **5**, R_3 = $(CH_2)_2$-3, 4-$(CH_3O)_2C_6H_3$ and $n = 1$ was examined with respect to a variation of a substituent in the para position of an R_1 phenyl. The equation $\log (1/C_{175}) = 2.85 - 0.67(MR) + 0.033(MR)^2$ ($n = 9$, $F = 5.9$, $r^2 = 0.66$, and s = 0.77) was obtained.

A third group, **4**, $n = 1$ and R_1 = Ph, was examined with respect to substituents on an R_3 phenethyl group, but no significant correlation could be determined.

Structural comparison of the 2-ethynylbenzenealkanamines with other known calcium entry blockers show some areas of possible similarity. For example, the structural function of an alkoxyphenethyl group on nitrogen could parallel a similar function in compounds related to verapamil. Clarification of the structural relationship between basic calcium entry blockers will need to await detailed binding studies.

On the basis of the profile in SHR, which includes no increase in heart rate, no significant effect on salt–water balance, no dysrhythmic events, and a sustained decrease in blood pressure, compound **5b** was chosen for clinical testing as an antihypertensive agent.

Compound **4a** was selected for further development as an antiaginal agent. The selection of **4a** was based on its potency, its ability to elevate coronary flow while decreasing oxygen demand in a dog model,[21] and its selectivity for the coronary circulation in a rat microsphere model. The supply and demand dog model[22] and the microsphere rat model[23] have been described in the literature.

Experimental Section

Melting points were taken on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian EM390 (90 MHz) or a Bruker WM-360 (360 MHz) spectrometer with $CDCl_3$ as solvent and $(CH_3)_4Si$ as an internal standard. ^{13}C NMR spectra were recorded on a JEOL FX60-Q (15.1 MHz) spectrometer. IR spectra were obtained on a Perkin-Elmer 521, 283, or 727B spectrophotometer in KBr pellets. Mass spectra were obtained on a VG Micro Mass 7035 or a Finnegan Model 9500-3300-1600 instrument. TLC separations were carried out on silica gel plates with visualization by UV or I_2. Chemical microanalyses were determined by Atlantic Microlab, Inc. Atlanta, GA, or by Scandinavian Labs, Herlev, Denmark.

3-Methoxyphenylacetic acid was obtained from the Aldrich Chemical Co. 3-Methoxyphenylproponic acid was obtained from the Alpha Chemical Co.

Statistical Treatment of Vasodilator Data. Analyses were performed by using a program LANGEN, prepared for the DEC 10 System. This program performs analyses on data collected after infusing guinea pig hearts with various concentrations of the compounds being tested. Three parameters were measured: force (in grams), rate (in beats/minute) and flow (in milliliters/minute). Analysis (for all three parameters) includes means and standard errors of the raw data, means and standard errors of percent control values, and paired *t* tests and probabilities using the raw data. Additional analysis includes a nonlinear regression on the percent of control values for force and a linear regression on the percent of control values for flow. Up to four derived values are determined on the basis of the results of the regressions.

With use of the results of the linear regression on flow values, the concentrations that produce 175% of control for flow are reported (C_{175}) if they lie within the range of drug concentrations measured.

The effect on inotropy at the concentration producing 175% of control flow (C_{175}) is determined by calculating the corresponding dependent value on the force regression line (Ei) as a percent of control.

1-(2-Iodo-5-methoxyphenyl)-2-propanone (2a) (Procedure a). Samples of I_2 (101.6 g, 0.40 mol) and AgOAc (66.8 g, 0.40 mol) were added in portions to a solution of 65.7 g (0.40 mol) of **1a** in 400 mL of HOAc. The mixture was stirred 3 h. The AgI was removed by filtration and washed with HOAc. The filtrate was poured into ice water and the precipitated solid collected by filtration and washed with H_2O. The solid was dissolved in Et_2O and the Et_2O solution washed successively with H_2O, NaOH solution, $Na_2S_2O_3$ solution, and brine. The Et_2O solution was dried ($MgSO_4$) and concentrated to dryness. The residue was crystallized from hexane and a second crop taken. The total yield was 70.92 g (61%) of white solid: mp 58–59 °C; ^1H NMR ($CDCl_3$) δ 2.20 (s, 3 H, CCH_3), 3.75 (s, 3 H, CH_3O), 3.80 (s, 2 H, CH_2), 6.55 (dd, J = 3 and 8.5 Hz, 1 H, phenyl), 6.75 (d, J = 3 Hz, 1 H, phenyl), 7.65 (d, J = 8.5 Hz, 1 H, phenyl); mass spectrum (EI), m/z 290, 247, 163. Anal. ($C_{10}H_{11}IO_2$) C, H.

4-(2-Iodo-5-methoxyphenyl)-2-butanone (2b). This compound was prepared as above from 4-(3-methoxyphenyl)-2-butanone: mp 48–49 °C (82%); mass spectrum (EI), m/z 304, 177, 134. Anal. ($C_{11}H_{13}O_2$) C, H.

1-[5-Methoxy-2-(phenylethynyl)phenyl]-2-propanone (3a) (Procedure b). Samples of 6.0 g (5.2 mmol) of $(Ph_3P)_4Pd(0)$ and 2.0 g (10.3 mmol) of CuI were added to a deoxygenated solution of 150 g (0.517 mol) of **2a** and 68.1 mL (0.621 mol) of phenylacetylene in 1.8 L of Et_3N and 200 mL of THF under Ar. The mixture was stirred for 66 h at 25 °C. The mixture was filtered and the filtrate concentrated to dryness in vacuo. The residue was recrystallized from MeOH to give 115.4 g of solid. The solid was distilled in a Kügelrohr apparatus (150–190 °C, 0.05 Torr) to give 93.8 g of **3a**. The mother liquors from the crystallization were concentrated to dryness in vacuo. The residue was distilled

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in a Kügelrohr apparatus and the distillate recrystallized twice from MeOH to give an additional 18.0 g of **3a**: total yield, 82%; mp 63–64 °C; mass spectrum (EI), *m/z* 264, 221, 178. Anal. ($C_{18}H_{16}O_2$) C, H.

4-[5-Methoxy-2-(phenylethynyl)phenyl]-2-butanone (3b). This compound was prepared as above with **2b** as the starting material: mp 49–51 °C (87%); mass spectrum (EI), *m/z* 278, 235, 220, 203, 191, 178. Anal. ($C_{12}H_{15}O_2$) C, H.

***N*-[2-(3,5-Dimethoxyphenyl)ethyl]-5-methoxy-α-methyl-2-(phenylethynyl)benzeneethanamine (*E*)-2-Butenedioate (2:1) (4a) (Procedure d).** A 60-g sample of 5A molecular sieves was suspended in 100 mL of toluene, and 8.5 g (32 mmol) of **3a** and 5.82 g (32 mmol) of 3,5-dimethoxyphenethylamine were added. The mixture was stirred for 2 days at room temperature. The sieves were filtered and washed with toluene. The solvent was evaporated in vacuo. The residue was taken up in 50 mL of MeOH and 0.4 g (10.6 mmol) of $NaBH_4$ (pellet) was added. After 90 min, H_2O was added. The mixture was partitioned between CH_2Cl_2 and H_2O. The organic solution was washed with 3 N HCl, NaOH solution, and H_2O. The solution was dried (K_2CO_3) and the solvent evaporated in vacuo. The residue was taken up in MeOH and 2.76 g of fumaric acid added. The solid was collected and recrystallized from MeOH. There was obtained 8.12 g (56%): mp 186–188 °C; ^1H NMR (Me_2SO) δ 1.03 (d, *J* = 6 Hz, 3 H, CCH_3), 2.62–2.82 (m, 4 H, CH_2), 2.91–3.04 (q, *J* = 6, 2 H, CH_2), 3.11–3.23 (m, 1 H, CH), 3.69 (s, 6 H, OCH_3), 3.77 (s, 3 H, CH_3O), 6.32 (t, *J* = 2.2 Hz, 1 H, phenyl), 6.35 (d, *J* = 2.2 Hz, 2 H, phenyl), 6.48 (s, 1 H, fumarate), 6.82–6.90 (m, 2 H, phenyl), 7.32–7.37 (m, 3 H, phenyl), 7.43–7.51 (m, 3 H, phenyl); mass spectrum (EI), *m/z* 429, 208. Anal. ($C_{28}H_{31}NO_3 \cdot 0.5C_4H_4O_4 \cdot 0.25H_2O$) C, H, N, H_2O.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-5-methoxy-α-methyl-2-(phenylethynyl)benzenepropanamine Hydrochloride (4b) (Procedure f).** A solution of 5.0 g (18.0 mmol) of **3b**, 3.2 mL (18.9 mmol) of 2-(3,4-dimethoxyphenyl)ethylamine, and 34 mg (0.18 mmol) of *p*-toluenesulfonic acid in 150 mL of toluene was heated under reflux for 20 h with azotropic removal of H_2O. The solvent was evaporated. The residue was dissolved in 30 mL of MeOH and 0.80 g (21.1 mmol) of $NaBH_4$ pellets was added. The mixture was stirred for 2 h and 2.0 mL of HOAc was added. The mixture was stirred for 10 min and partitioned between Et_2O and 3 N NaOH. The organic solution was washed with H_2O and brine, dried (K_2CO_3), and concentrated to dryness. The residue was combined with 1.5 g of oxalic acid in hot 2-PrOH. The solid was collected and recrystallized from MeOH to give 6.26 g of the oxalate salt. The oxalate salt was converted to free base and an HCl salt prepared by addition of ethereal HCl to an Et_2O solution of the base. It was recrystallized from CH_3CN/Et_2O to give 3.92 g (43%): mp 128–130 °C; ^1H NMR ($CDCl_3$) δ 1.52 (d, *J* = 6 Hz, 3 H, CCH_3), 2.7–3.6 (m, 9 H, CH_2, CH), 3.66 (s, 6 H, OCH_3), 3.72 (s, 3 H, OCH_3), 6.42–6.75 (m, 5 H, phenyl), 7.1–7.4 (m, 6 H, phenyl), 9.7 (br s, 1 H, NH^+); mass spectrum (EI), *m/z* 443, 293. Anal. ($C_{29}H_{33}NO_3 \cdot HCl$) C, H, N.

***N*-[2-[5-Methoxy-2-(phenylethynyl)phenyl]-1-methylethyl]-1-naphthaleneethanamine Hydrochloride Hydrate (1:1:0.33) (4d) (Procedure c).** A 4.33-g (0.064 mol) sample of $NaBH_3CN$ was added to a solution of 13.0 g (0.049 mol) of **3a** and 9.23 g (0.054 mol) of 2-(1-naphthyl)ethylamine in 120 mL of MeOH under Ar. The mixture was stirred for 72 h. A solution of MeOH/HCl was added to bring the pH to 1. The mixture was stirred 1 h and concentrated to dryness. The residue was partitioned between Et_2O and NaOH. The Et_2O layer was washed with brine, dried (K_2CO_3), and concentrated to dryness. The residue was flash chromatographed on SiO_2 with acetone/hexane (1:3) as eluent. There was obtained 15 g of the major product as a yellow oil. It was converted to a hydrochloride salt from ethereal HCl. There was obtained 14.3 g of a crystalline solid (60%): mp 107–110 °C; ^1H NMR ($CDCl_3$) δ 1.5 (d, *J* = 6, 3 H, CCH_3), 3.1–3.6 (m, 4 H, CH_2), 3.5–4.0 (m, 3 H, CH_2, CH), 3.8 (s, 3 H, OCH_3), 6.6–7.4 (m, 12 H, aromatic), 7.4–7.8 (m, 2 H, aromatic), 8.0–8.2 (m, 1 H, aromatic), 10.1 [s, (br), 1 H, N^+H]; mass spectrum (EI), *m/z* 419, 402, 278, 198, 155. Anal. ($C_{30}H_{29}NO \cdot 0.33H_2O$) C, H, N, H_2O.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-5-methoxy-*N*,α-dimethyl-2-(phenylethynyl)benzenepropanamine Hydrochloride (5b) (Procedure g).** A 0.4-g pellet of $NaBH_4$ was added to a solution of 2.92 g (6.6 mmol) of the free base of **4b** and 5 mL of formalin in 50 mL of MeOH under Ar. The mixture was stirred for 20 min. Glacial HOAc was added to pH 5. The mixture was partitioned between CH_2Cl_2 and 1 N NaOH. The organic solution was washed with H_2O and brine and dried ($MgSO_4$) and the solvent evaporated. An oxalate salt was prepared out of MeOH (3.39 g, 88%, mp 150–153 °C). The oxalate was converted to free base. A hydrochloride salt was prepared from Et_2O/HCl and recrystallized from 2-PrOH: mp 116–122 °C; ^1H NMR ($CDCl_3$) δ 1.42 [d, *J* = 6.5 Hz, 1 H, CCH_3 (diastereomers due to NH^+)], 1.59 (d, *J* = 6.5 Hz, 2 H, CCH_3), 2.33 (q, *J* = 9 Hz, 0.67 Hz, CH_2), 2.61 (s, 2 H, NCH_3), 2.62 (s, 1 H, NCH_3), 3.3–2.7 (m, 7 H, CH_2), 3.36 (m, 1 H, CH), 3.82 (s, 9 H, OCH_3), 6.59–6.86 (m, 5 H, phenyl), 7.24–7.34 (m, 3 H, phenyl), 7.38–7.46 (m, 3 H, phenyl), 12.2 (br s, 1 H, NH^+); mass spectrum (EI), *m/z* 457, 456, 306. Anal. ($C_{30}H_{35}NO_3 \cdot HCl$) C, H, N.

2-Iodo-5-methoxy-*N*,*N*-dimethylbenzeneacetamide (9a) (Procedure l). A 16.7-g (0.19 mol) sample of oxalyl chloride was added dropwise at 0 °C to a solution of 50.0 g (0.17 mol) of 2-iodo-5-methoxybenzeneacetic acid in 310 mL of dry toluene and 31.7 mL of DMF. The mixture was allowed to warm to room temperature and to stir for 16 h. The solution was cooled to 0 °C and $(CH_3)_2NH$ gas was admitted until the mixture was strongly basic. The mixture was allowed to warm to room temperature and to stir for 3 h and CH_2Cl_2 was added. The organic layer was washed with H_2O, 3 N HCl, and 3 N NaOH. The organic layer was dried ($MgSO_4$) and evaporated to dryness to give 54.2 g (80%) of a crystalline solid: mp 86–89 °C; ^1H NMR δ 2.3–3.3 (m, 4 H, CH_2), 3.0 (s, 6 H, NCH_3), 3.7 (s, 3 H, OCH_3), 6.8–8.2 (m, 3 H, phenyl); mass spectrum (EI), *m/z* 333, 332, 260, 206, 191. Anal. ($C_{10}H_{14}INO_2$) C, H.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-iodo-5-methoxy-*N*-methylbenzenepropanamide (9b).** The preparation was carried out as above with **8b** as the starting material to give a yellow oil (100%): ^1H NMR ($CDCl_3$) δ 2.36 [t, *J* = 7 Hz, 0.9 H, CH_2 (conformer)], 2.53 (t, *J* = 7 Hz, 1.1 H, CH_2), 2.69 (t, *J* = 7 Hz, 1.1 H, CH_2), 2.75 (t, *J* = 7 Hz, 0.9 CH_2), 2.83 (s, 1.65 H, NCH_3), 2.92 (t, *J* = 7 Hz, 0.9 H), 2.93 (s, 1.35 H, NCH_3), 2.98 (t, *J* = 7 Hz, 1.1 H), 3.42 (t, *J* = 7 Hz, 1.1 H, CH_2), 3.54 (t, *J* = 7 Hz, 1.1 H), 3.42 (t, *J* = 7 Hz, 1.1 H, CH_2), 3.54 (t, *J* = 7 Hz, 0.9 H, CH_2), 3.82 (s, 6 H, OCH_3), 6.45–6.8 (m, 5 H, phenyl), 7.71 (t, *J* = 9 Hz, 1 H, phenyl); exact mass spectrum calcd for $C_{21}H_{26}INO_4$ 483.090, found 483.083.

2-Iodo-5-methoxy-*N*,*N*-dimethylbenzenepropanamide (9f). The preparation was carried out as above, starting with **8b** to give a yellow oil in 74% yield. Anal. ($C_{12}H_{16}INO_2$) C, H.

2-Iodo-5-methoxy-*N*,*N*-dimethylbenzeneethanamine Hydrochloride (10a) (Procedure m). A solution of 80.8 g (0.253 mol) of **9a** in 800 mL of THF was added over 10 min to 760 mL of 1 M BH_3 in THF. The mixture was heated under reflux for 2 h. A 50-mL portion of H_2O was added and the mixture stirred. The solvent was evaporated and 200 mL of propanoic acid was added. The mixture was heated at 80 °C for 2 h, poured onto ice/NaOH, and extracted with Et_2O. The Et_2O solution was washed with NaOH and H_2O and dried (K_2CO_3). The Et_2O was evaporated to give 67.3 g of an oil, which was distilled in a Kügelrohr apparatus at 125–150 °C (0.17 Torr). The distillate was taken up in 3 N HCl and washed with Et_2O. The aqueous layer was made basic with 3 N NaOH and extracted with Et_2O. The ether solution was dried (K_2CO_3) and evaporated to give 58.6 g (76%) of a colorless oil. The hydrochloride was prepared out of Et_2O/HCl and recrystallized form 2-PrOH: mp 168–169 °C; ^1H NMR ($CDCl_3$) δ 2.5 (s, 6 H, NCH_3), 2.5–3.3 (m, 4 H, CH_2), 3.7 (s, 3 H, OCH_3), 6.2–7.8 (m, 3 H, phenyl); mass spectrum (EI), *m/z* 305, 304, 278, 262, 247, 219. Anal. ($C_{11}H_{16}INO \cdot HCl$) C, H.

5-Methoxy-*N*,*N*-dimethyl-2-(phenylethynyl)benzeneethanamine (11a) (Procedure j). A mixture of 15.0 g (0.049 mol) of **10a** and 12.1 g of copper(I) phenylacetylide in 150 mL of dry pyridine was heated under reflux under N_2 for 18 h. The pyridine was evaporated in vacuo. The residue was triturated with NH_4OH solution and Et_2O. The Et_2O layer was washed with brine, dried, and concentrated to dryness. A hydrochloride salt was prepared from Et_2O/HCl and recrystallized successively from 2-PrOH and EtOH. There was obtained 6.9 g (44%) of a solid: mp 190–191 °C; mass spectrum (EI), *m/z* 279, 235, 178. Anal. ($C_{19}H_{21}NO \cdot HCl$) C, H.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-5-methoxy-*N*-methyl-2-(phenylethynyl)benzenepropanamine Hydrochloride Hydrate (8:8:1) (11b) (Procedure k).** A solution of 11.62 mL (19.6 mmol) of *n*-BuLi (1.6 N in hexane) was added to a solution of 2.09 mL (19.0 mmol) of phenylacetylene in 15 mL of THF at 0 °C under Ar. The mixture was stirred for 15 min and transferred via cannula to a flask containing 2.53 g (18.6 mmol) of anhydrous $ZnCl_2$ while the temperature was maintained at 0 °C. The mixture was stirred for 15 min. A solution of 7.27 g (15.5 mmol) of **10b** and 0.36 g (0.31 mmol) of $[Ph_3P]_4Pd(0)$ in 100 mL of THF was added. The mixture was allowed to warm to room temperature and to stir for 3.5 h. The mixture was partitioned between H_2O and CH_2Cl_2. The organic phase was washed with 5% HCl and 5% NaOH, dried (K_2CO_3), and concentrated to an oil. The residue was dissolved in MeOH, cooled, and filtered. The filtrate was concentrated. The residue was taken up in MeOH and methanolic hydrogen chloride added to pH 7. The solvent was evaporated and the residue crystallized from *t*-BuOH/Et_2O. The solid was recrystallized from *t*-BuOH/Et_2O to give 4.02 g (56%) of a white solid: mp 122–123 °C. Anal. ($C_{29}H_{33}NO_3 \cdot HCl \cdot {}^1/_8H_2O$) C, H, N, H_2O.

4-(2-Bromo-5-fluorophenyl)-2-butanone (14). A solution of 16.0 g (0.085 mol) of 2-bromo-5-fluorotoluene, 15.1 g (0.085 mol) of *N*-bromosuccinimide, and 0.16 g (0.66 mmol) of benzoyl peroxide in 50 mL of CCl_4 was heated under reflux and irradiated with a 150-W flood lamp under Ar for 3 h. The mixture was cooled and the solid filtered. Evaporation of the solvent from the filtrate gave 21.2 g (93%) of an oil containing approximately 61% of the benzyl bromide, 19% of the unreacted starting toluene, and 20% of the benzal bromide: ^1H NMR ($CDCl_3$) δ 7.8–6.7 (m, relative area 1.00, Ar *H* plus C*H* Br_2), 4.51 (s, relative area 0.342, Ar CH_2 Br), 2.40 (s, relative area 0.157, Ar CH_3).

The crude benzyl bromide (48 mmol), 8.2 mL (0.79 mmol) of 2,4-pentanedione, and 10.9 g (7.9 mmol) of K_2CO_3 were added to 75 mL of EtOH, and the mixture was heated under reflux for 16 h. The solid was filtered and the solvent was evaporated from the filtrate. The resulting oil was flash chromatographed on SiO_2 with EtOAc/hexane to give after evaporation of solvent 7.9 g of a yellow oil (67%). Anal. ($C_{10}H_{10}BrFO$) C, H.

1-[2-(Phenylethynyl)phenyl]-2-propanone (19). This compound was prepared from 1-(2-bromophenyl)-2-propanone (18) as described for **3a** (59%): mp 60–61 °C. Anal. ($C_{17}H_{14}O$) C, H.

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Registry No. **1a**, 3027-13-2; **1b**, 29114-51-0; **2a**, 99254-54-3; **2b**, 99254-53-2; **3a**, 99255-23-9; **3b**, 112399-16-3; **4a**, 99256-57-2; **4a**·O·5$C_4H_4O_4$, 99256-58-3; **4b**, 99256-46-9; **4b**·HCl, 99256-29-8; **4b**·O·5$C_5H_2O_4$, 112399-17-4; **4c**, 99256-63-0; **4c**·O·5$C_4H_4O_4$, 99256-64-1; **4d**, 112399-18-5; **4d**·HCl, 112399-19-6; **4e**, 99256-42-5; **4e**·HCl, 99256-23-2; **4f**, 99255-06-8; **4f**·HCl, 112399-20-9; **4g**, 99256-46-9; **4g**·HCl, 99256-29-8; **4h**, 99255-02-4; **4h**·O·5$C_4H_4O_4$, 99255-03-5; **4i**, 112399-21-0; **4i**·HCl, 112399-22-1; **4j**, 99256-13-0; **4j**·O·5$C_4H_4O_4$, 99256-14-1; **4k**, 99256-15-2; **4k**·O·5$C_4H_4O_4$, 112399-23-2; **5a**, 99256-81-2; **5a**·HCl, 99256-71-0; **5b**, 99254-95-2; **5b**·HCl, 99254-96-3; **5c**, 99256-80-1; **5c**·HCl, 99256-68-5; **5d**, 112399-24-3; **5d**·HCl, 112399-25-4; **5e**, 99256-44-7; **5e**·HCl, 99256-25-4; **5f**, 99255-28-4; **5f**·$C_4H_4O_4$, 99255-29-5; **5g**, 99256-76-5; **5g**·$C_4H_4O_4$, 99256-77-6; **5h**, 99255-26-2; **5h**·$C_4H_4O_4$, 99255-27-3; **5i**, 112399-26-5; **5i**·HCl, 112399-27-6; **5l**, 99256-41-4; **5l**·HCl, 99256-20-9; **5m**, 112399-28-7; **5m**·O·5$C_4H_4O_4$, 112399-29-8; **5n**, 99256-89-0; **5n**·O·5$C_4H_4O_4$, 99256-90-3; **5o**, 99255-52-4; **5o**·O·5$C_4H_4O_4$, 99255-53-5; **5p**, 99255-61-5; **5p**·HCl, 99255-55-7; **5q**, 99255-62-6; **5q**·HCl, 99255-56-8; **5r**, 99255-59-1; **5s**, 99255-57-9; **5s**·$C_4H_4O_4$, 112399-30-1; **5t**, 99255-60-4; **5u**, 99255-40-0; **5u**·HCl, 99255-42-2; **5v**, 99255-20-6; **5v**·HCl, 99255-21-7; **5w**, 99256-56-1; **5w**·HCl, 99256-55-0; **5x**, 99540-07-5; **5x**·$C_4H_4O_4$, 112399-31-2; **6g**, 99256-50-5; **6g**·HCl, 99255-82-0; **6h**, 99254-77-0; **6h**·HCl, 99254-78-1; **6i**, 112399-32-3; **6i**·$C_2H_2O_4$, 112399-33-4; **6j**, 99255-80-8; **6v**, 112399-34-5; **6w**, 112399-35-6; **7h**, 99255-51-3; **7h**·$C_2H_2O_4$, 100634-30-8; **7j**, 99255-95-5; **7j**·$C_2H_2O_4$, 112399-36-7; **7v**, 99254-84-9; **7v**·$C_2H_2O_4$, 112399-37-8; **7w**, 99255-66-0; **7w**·HCl, 112421-53-1; **8a**, 73029-52-4; **8a** acid chloride, 112399-38-9; **8b**, 99254-50-9; **8b** acid chloride, 99254-55-4; **9a**, 99540-20-2; **9b**, 99254-56-5; **9f**, 99540-24-6; **10a**, 99540-37-1; **10a**·HCl, 99540-38-2; **10b**, 99254-62-3; **10b**·$C_7H_8SO_3$, 99482-66-3; **10f**, 112399-39-0; **10f**·HCl, 99540-40-6; **11a**, 99540-02-0; **11a**·HCl, 99540-58-6; **11b**, 99254-93-0; **11b**·HCl, 99254-94-1; **11c**, 100634-48-8; **11c**·2$C_6H_{13}NSO_3$, 112399-40-3; **11d**, 100634-45-5; **11e**, 100634-41-1; **11e**·2$C_6H_{13}NSO_3$, 112421-54-2; **11f**, 99540-59-7; **11f**·$C_4H_4O_4$, 99540-60-0; **12**, 112399-41-4; **12**·HCl, 112399-42-5; **13**, 99256-11-8; **14**, 112399-43-6; **15**, 112399-44-7; **15**·HCl, 112399-45-8; **16**, 112399-46-9; **16**·$C_2H_2O_4$, 112399-47-0; **17**, 112399-48-1; **17**·HCl, 112399-49-2; **18**, 21906-31-0; **19**, 99255-22-8; **20**, 99255-37-5; $H_2N(CH_2)_2$-3,5-$(CH_3O)_2C_6H_3$, 3213-28-3; H_2N-3,4-$(CH_3O)_2C_6H_3$, 120-20-7; H_2N-2,3-$(CH_3O)_2C_6H_3$, 3213-29-4; $H_2N(CH_2)_2Ph$, 64-04-0; $H_2N(CH_2)_4Ph$, 13214-66-9; $H_2N(CH_2)_3Ph$, 2038-57-5; $H_2N(CH_2)_2$-3-$CH_3OC_6H_4$, 2039-67-0; $H_2N(CH_2)_2$-1-naphthyl, 4735-50-6; $H_2N(CH_2)_2$-3-ClC_6H_4, 13078-79-0; $H_2N(CH_2)_2$-3,4-$Cl_2C_6H_3$, 21581-45-3; $H_2N(CH_2)_2$-2,3-$Cl_2C_6H_3$, 34164-43-7; $H_2N(CH_2)_2$-4-$NO_2C_6H_4$, 24954-67-4; $H_2N(CH_2)_2$-4-ClC_6H_4, 156-41-2; 4-$ClC_6H_4C{\equiv}CH$, 873-73-4; 4-$CF_3C_6H_4C{\equiv}CH$, 705-31-7; 4-$NCC_6H_4C{\equiv}CH$, 3032-92-6; 4-$CH_3OC_6H_4C{\equiv}CH$, 99255-63-7; 4-$(CH_3)_2NC_6H_4C{\equiv}CH$, 17573-94-3; 4-$FC_6H_4C{\equiv}CH$, 766-98-3; $PhC{\equiv}CH$, 536-74-3; $Ph(CH_2)_2C{\equiv}CH$, 16520-62-0; *n*-$C_4H_9C{\equiv}CH$, 693-02-7; 2-bromo-5-fluorobenzenethanol acetate, 112399-43-6; 2-bromo-5-fluorotoluene, 452-63-1; 2-bromo-5-fluorobenzyl bromide, 112399-50-5; 2-bromo-5-fluorobenzal bromide, 112399-51-6; *p*-ethynylcumene, 23152-99-0.