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Studies on Quinazolines and 1,2,4-Benzothiadiazine 1,1-Dioxides. 8.[1,2] Synthesis and Pharmacological Evaluation of Tricyclic Fused Quinazolines and 1,2,4-Benzothiadiazine 1,1-Dioxides as Potential α_1-Adrenoceptor Antagonists

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A series of 2-substituted methyl 2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-ones (**4**), 3-substituted methyl 2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-ones (**5**), 3-substituted methyl 2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-ones (**15a**,**b**), 3-substituted methyl 2,3-dihydroimidazo-[2,1-*b*]quinazolin-5(1*H*)-ones (**16a**,**b**), 3-substituted methyl 2,3-dihydro-1*H*-imidazo[1,2-*b*][1,2,4]benzothiadiazine 5,5-dioxides (**33a**,**b**), 2-substituted methyl imidazo[1,2-*c*]quinazolin-5(6*H*)-ones (**42**−**45a**,**b**), 3-substituted methyl imidazo[1,2-*c*]quinazolin-5(6*H*)-ones (**50**−**53a**,**b**), 3-substituted methyl 5*H*-thiazolo[2,3-*b*]quinazolin-5-ones (**55**−**56a**,**b**), and 3-substituted methyl 5-(methylthio)-2,3-dihydroimidazo[1,2-*c*]quinazoline (**57**) were synthesized as compound **1** conformational rigid congeners for pharmacological evaluation as potential α_1-adrenoceptor antagonists. Compounds **4, 5, 33a**,**b**, **44a**,**b**, **45a**,**b**, **52a**,**b**, **53a**,**b**, and **57** were found to possess high affinity for the α_1-adrenoceptor. Compounds **5** and **57** were the most highly selective and potent α_1 antagonists with $K_i = 0.21 \pm 0.02$ and 0.90 ± 0.08 nM, respectively. The *S*-enantiomers of these two compounds ($K_i = 0.13 \pm 0.01$ nM for (*S*)-(−)-**5**; $K_i = 1.0 \pm 0.2$ nM for (*S*)-(+)-**57**) were 144−200-fold more potent than the *R*-enantiomers ($K_i = 26 \pm 8$ nM for (*R*)-(+)-**5**; $K_i = 144 \pm 23$ nM for (*R*)-(−)-**57**). Compound **4** showed 8-fold higher affinity to α1A-AR better than α1B-AR. These compounds possessed weak to no activity against the 5-HT1A receptor.

Introduction

Blocking the action of adrenergic neurotransmitters on the α_1-adrenoceptor is a well-known approach for the clinical treatment of hypertension.[3] It was recently reported that the antihypertensive effects of several α_1-adrenoceptor antagonists were associated with favorable changes in serum cholesterol profiles,[4] and there are several α_1-antagonists currently being studied for the treatment of dysuria secondary to benign prostatic hypertrophy.[5] The quinazoline-2,4-dione derivative **1**,[6] which possesses a ((2-methoxyphenyl)piperazinyl)ethyl side chain at the 3-position, is a potent antihypertensive agent that acts via the α_1-adrenoceptor. A literature survey revealed that the addition of a (2-methoxyphenyl)piperazine side chain onto different heterocycles, such as thienopyrimidinediones (**2**)[7] and pyrimido[5,4-*b*]indole (**3**) derivatives,[8] provides compounds that effectively lower blood pressure by antagonizing the α_1-adrenoceptor. Our laboratories are interested in preparing unique cardiovascular agents based on the quinazoline ring system.[9] Addition of a (2-methoxyphenyl)piperazine side chain at the 2- or 3-position of the angular tricyclic 2,3-dihydroimidazo[1,2-*c*]quinazoline ring system of SGB-1534 resulted in the formation of potent antihypertensive agents such as 2-[[4-(2-methoxyphenyl)piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-*c*]-quinazolin-5(6*H*)-one (**4**) and 3-[[4-(2-methoxyphenyl)-piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-*c*]-quinazolin-5(6*H*)-one (**5**) that selectively antagonized the α_1-adrenoceptor.[9] However, the stereochemical effect of the substituent in compounds **4** and **5** on the binding affinity to the α_1-adrenoceptor has not been studied. Furthermore, 2-[[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-1,2,4-benzothiadiazin-3(4*H*)-one 1,1-dioxide (**6**),[10] a bioisostere formed by replacing the quinazoline ring system with 1,2,4-benzothiadiazine 1,1-dioxide, was synthesized and characterized as a potent antihypertensive agent. On the basis of these active molecules, we presumed that the 1-arylpiperazine side chain might be an essential moiety for lowering blood pressure.[11] Thus, the conformational effects of 2,3-dihydroimidazo[1,2-*c*]quinazoline derivatives such as

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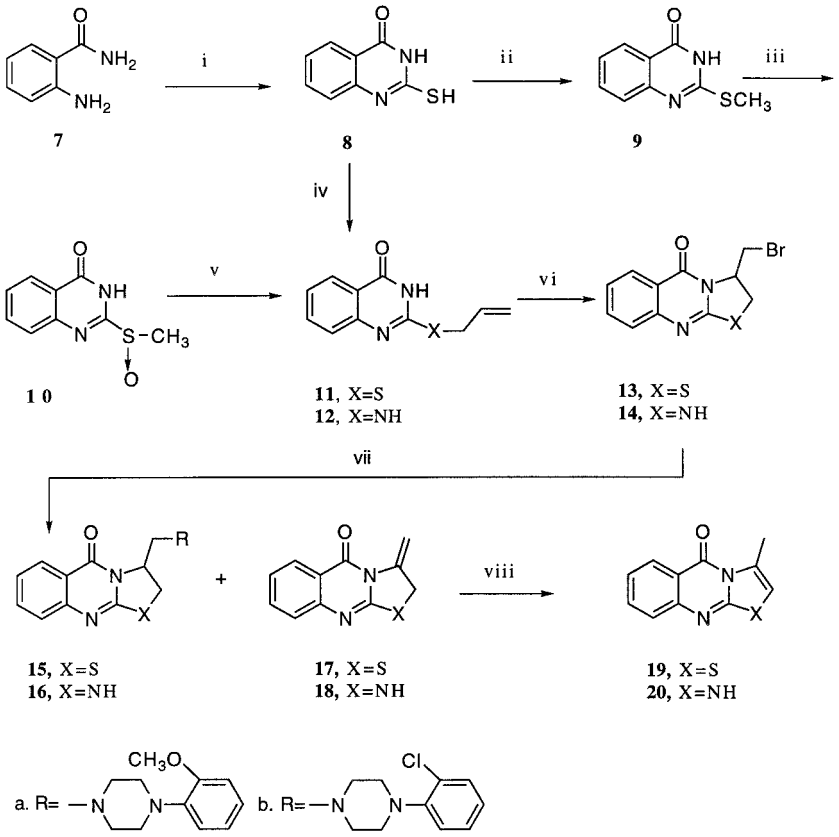
Scheme 1[a]



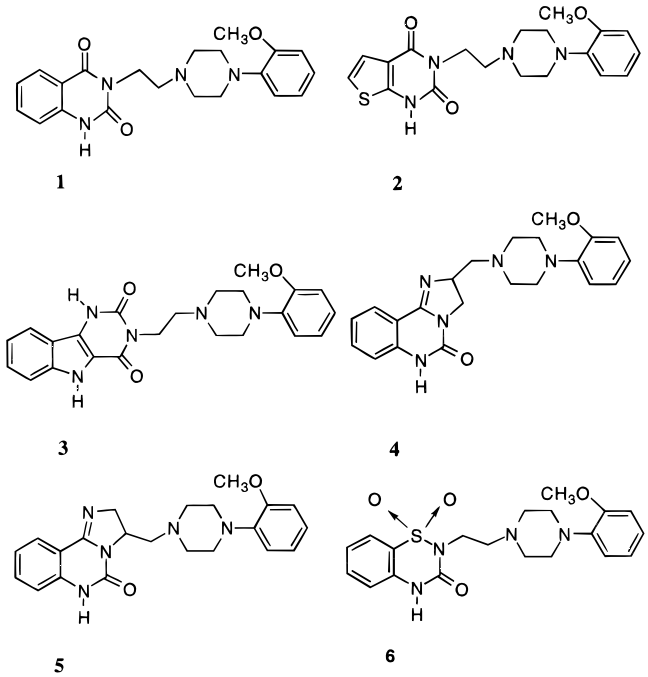
[a] (i) CS_2, NaOH, ethanol/water (5/1), reflux, 24 h, 86%; (ii) CH_3I, H_2O, rt, 76%; (iii) 60% mCPBA, $CHCl_3$, rt, 1 h, 85%; (iv) allyl bromide, NaOH, H_2O, rt, 30 min, 98% for **11**; (v) allylamine hydrochloride, $NaHCO_3$, CH_3CN, reflux, 1 h, 78% for **12**; (vi) NBS, THF, rt, 30 min, 96% for **13**, 93% for **14**; (vii) 4-(2-substituted phenyl)-1-piperazine HCl, $NaHCO_3$, reflux, 48 h, 16% for **15a** and 70% for **17**, 50% for **16a** and 8.4% for **18**, 21% for **16b** and 48% for **18**; (viii) H_2SO_4, 45 °C, 20 min, 98%.

compounds **4** and **5** on the α_1-adrenoceptor were examined. In addition, the rigid coplanar tricyclic congeners of compounds **4** and **5** were also synthesized for pharmacological study in an attempt to reduce the freedom of the side chain on compounds **4** and **5**. This paper describes the synthesis and biological activity of these novel tricyclic compounds.

Chemistry

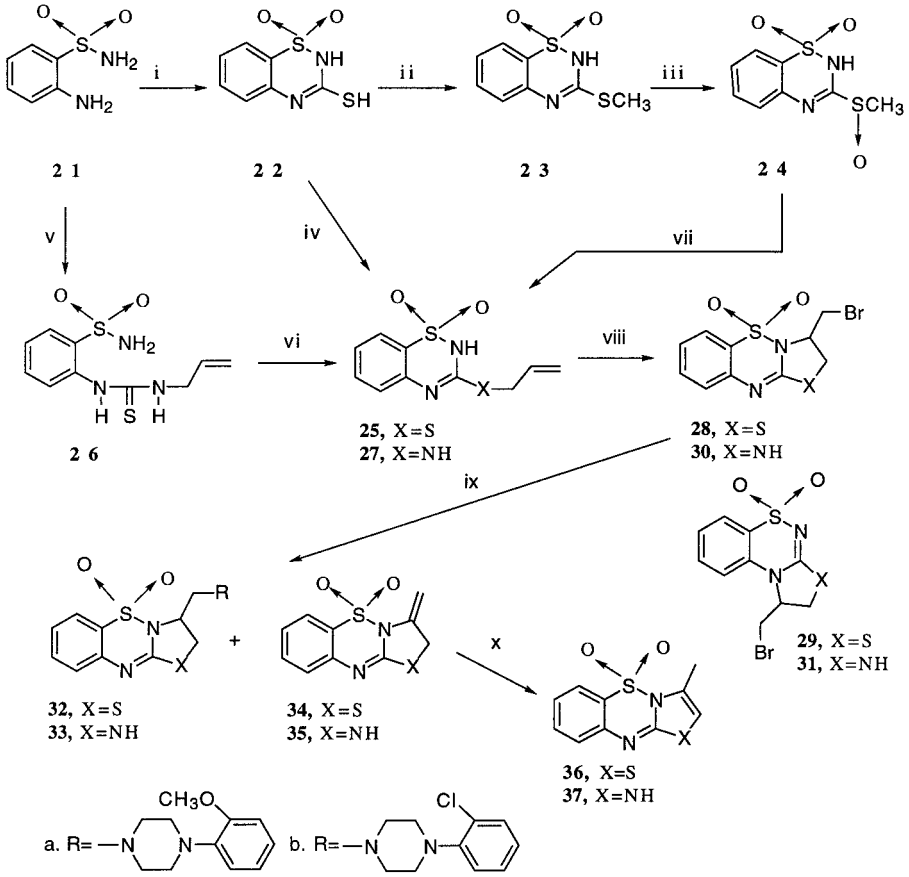
The preparation of tricyclic fused quinazolines and 1,2,4-benzothiadiazine 1,1-dioxides containing an arylpiperazine side chain was accomplished by the synthetic sequence depicted in Schemes 1 and 2. The key intermediates, 2-(allylthio)-4(3*H*)quinazolinones (**11**), 2-(allylamino)-4(3*H*)quinazolinones (**12**), 3-(allylthio)-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (**25**), and 3-(allylamino)-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (**27**) were first synthesized. It was reasoned that the bromocyclization of compounds **11**, **12**, **25**, and **27** with *N*-bromosuccinimide would follow Baldwin's rules[12] in which 5-exo-trig ring closure would provide the tricyclic quinazolinone or 1,2,4-benzothiadiazine 1,1-dioxide derivatives (**13**, **14**, **28**, and **30**) for the subsequent substitution reaction with arylpiperazines.

The starting material, 2-thioxo-1*H*,3*H*-quinazolin-4-one (**8**), which was prepared by condensation of anthranilamide (**7**) with carbon disulfide,[13] was treated with allyl bromide in aqueous sodium hydroxide solution to afford 2-(allylthio)-4(3*H*)-quinazolinone (**11**) in 98% yield. Compound **11** was subsequently reacted with



NBS at room temperature to furnish 3-(bromomethyl)-2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (**13**) in 96% yield. Treatment of **13** with 4-(2-methoxyphenyl)-1-piperazine in the presence of sodium bicarbonate at 50 °C afforded the desired product 3-[[4-(2-methoxyphenyl)piperazin-1-yl]methyl]-2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (**15**) in 16% yield and also produced

Scheme 2[a]



[a] (i) CS_2, $NaHCO_3$, ethanol/water (5/1), reflux, 24 h, 94%; (ii) CH_3I, Na_3CO_3, 99%; (iii) 30% H_2O_2, acetic acid, rt, 24 h, 79%; (iv) allyl bromide, NaOH, water, rt, 20 min, 93% for **25**; (v) allyl isothiocyanate, 2-propanol, rt, 48 h, 80%; (vi) $NaHCO_3$, reflux, 24 h, 51% for **27**; (vii) allylamine hydrochloride, K_2CO_3, CH_3CN, reflux, 1 h, 94% for **27**; (viii) NBS, THF, rt, 30 min, 71% for **28**, 72% for **30**; (ix) 4-(2-substituted phenyl)-1-piperazine HCl, $NaHCO_3$, reflux, 48 h, 46% for **33a**, 50% for **33b**; (x) H_2SO_4, 45 °C, 20 min, 90%.

3-methylene-2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (**17**) in 48% yield. Compound **17** was also prepared in 88% yield by refluxing **11** with 2 equiv of potassium carbonate in MIBK. The proton-catalyzed isomerization of **17** with sulfuric acid yielded 3-methyl-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (**19**).

An attempt to prepare 2-(allylamino)-4(3*H*)-quinazolinone (**12**) by treatment of 3-(methylthio)-4(3*H*)-quinazolinone (**9**)[14] with allylamine was unsuccessful; 2,4(1*H*,3*H*)-quinazolinedione was isolated as the sole product. This was probably due to the poor nucleophilicity of allylamine with the methylthio moiety serving as the leaving group. Oxidation of compound **9** in acetic acid with 30% hydrogen peroxide furnished 2,4(1*H*,3*H*)-quinazolinedione instead of 3-(methylsulfinyl)quinazolin-4(3*H*)-one (**10**). However, compound **10** was obtained in 85% yield when **9** was treated with *m*-chloroperbenzoic acid (mCPBA). Subsequent reaction of **10** with allylamine afforded compound **12** in 78% yield. Treatment of compound **12** with NBS in THF at room temperature gave 3-(bromomethyl)-2,3-dihydroimidazo-[2,1-*b*]quinazolin-5(1*H*)-one (**14**) in 93% yield. An analogous treatment of **14** with 4-(2-methoxyphenyl)-1-piperazine under identical conditions gave 3-[[4-(2-methoxyphenyl)piperzin-1-yl]methyl]-2,3-dihydroimidazo-[2,1-*b*]quinazolin-5(1*H*)-one (**16a**) in 50% yield and 3-methylene-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one (**18**) in 8.4% yield. Isomerization of **18** to 3-methylimidazo[2,1-*b*]quinazolin-5(1*H*)-one (**20**) under acidic conditions was unsuccessful.

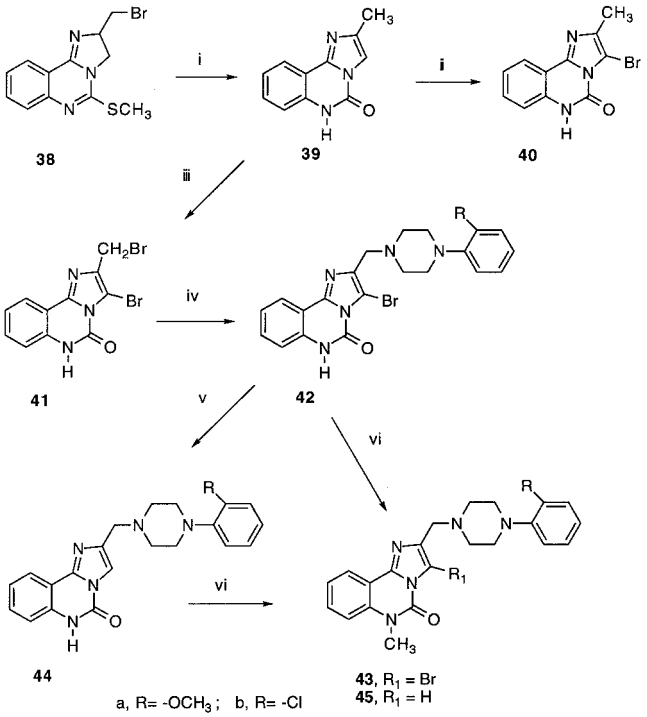
For the synthesis of tricyclic fused 4*H*-1,2,4-benzothiadiazine 1,1-dioxide derivatives, the starting material, 3-mercapto-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (**22**),[14] obtained by condensation of 2-aminobenzenesulfonamide with carbon disulfide, was reacted with allyl bromide to produce 3-(allylthio)-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (**25**) in 93% yield. Treatment of **25** with NBS afforded the linear 3-(bromomethyl)-2,3-dihydrothiazolo[3,2-*b*][1,2,4]benzothiadiazine 5,5-dioxide (**28**) in 71% yield instead of the angular **29**. The structural assignment of compound **28** was primarily based on ^{13}C NMR spectral data. The original ^{13}C NMR spectroscopic studies on the 3-substituted 1,2,4-benzothiadiazine 1,1-dioxides by Jakobsen and Treppendahl[15] provided a critical tool to distinguish between compounds alkylated at the C-2 and C-4 positions by examination of the chemical shift of C-4a in the benzothiadiazine 1,1-dioxide ring. For example, the chemical shift of C-4a in the 2-alkylated derivatives was found around 143 ppm, while that in the 4-alkylated compounds appeared between 135 and 138 ppm. The same phenomenon was applicable to the angular tricycles such as 2,4-dihydro-1*H*-imidazo[2,1-*c*][1,2,4]benzothiadiazine 5,5-dioxide, 2,3-dihydro-1*H*,5*H*-pyrimido[2,1-*c*]-[1,2,4]benzothiadiazine 6,6-dioxide,[16] and 2,3-dihydroxazolo[3,2-*b*][1,2,4]benzothiadiazine 5,5-dioxide[10] and the linear tricyclic ring systems such as in 2,3-dihydro-1*H*-

imidazo[1,2-*b*][1,2,4]benzothiadiazine 5,5-dioxide.[2,17] In fact, the chemical shift of C-9a (142.3 ppm) in the ^{13}C NMR spectrum of **28** is in good agreement with previously reported data of the 4-alkylated product and tricyclic fused 4*H*-2,4-benzothiadiazine 1,1-dioxide derivatives.[2,15] Compound **28** was reacted with 4-(2-methoxyphenyl)-1-piperazine to furnish 3-methylene-2,3-dihydrothiazolo[3,2-*b*][1,2,4]benzothiadiazine 5,5-dioxide (**34**) in 86% yield. The reaction failed to give the desired 3-[[4-(2-methoxyphenyl)piperazin-1-yl]methyl]-2,3-dihydrothiazolo[3,2-*b*][1,2,4]benzothiadiazine 5,5-dioxide (**32a**). The proton-catalyzed isomerization of compound **34** afforded 3-methylthiazolo[3,2-*b*][1,2,4]benzothiadiazine 5,5-dioxide (**36**) in 90% yield (Scheme 1).

3-(Methylthio)-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (**23**) was obtained in 99% yield by treatment of **22** with methyl iodide in the presence of aqueous sodium hydroxide. Unlike the oxidation of compound **9**, oxidation of compound **23** with 30% hydrogen peroxide produced a precipitate of 3-(methylsulfinyl)-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (**24**) in 79% yield on the basis of the ^1H NMR spectral data and elemental analysis. Compound **24** was treated with allylamine to afford compound **27** in 94% yield. Since we have previously reported that the reaction of 2-aminobenzenesulfonamide (**21**) with alkyl or aryl isothiocyanate led to the formation of 3-substituted amino-4*H*-1,2,4-benzothiadiazine 1,1-dioxide via elimination of hydrogen sulfide,[18] compound **27** was alternatively prepared by condensation of **21** with allyl isothiocyante in 2-propanol followed by ring closure of the resulting 2-(3-allylthioureido)-benzenesulfonamide (**26**) under basic conditions. Compound **27** was then subjected to bromocyclization with NBS to afford 3-(bromomethyl)-2,3-dihydro-1*H*-imidazo[1,2-*b*][1,2,4]benzothiadiazine 5,5-dioxide (**30**) in 72% yield. The chemical shift of C-9a (145.4 ppm) in the ^{13}C NMR spectrum of compound **30** was in good agreement with the previously reported data[2,17] of the 2,3-dihydro-1*H*-imidazo[1,2-*b*][1,2,4]benzothiadiazine 5,5-dioxide ring system. Treatment of **30** with 4-(2-methoxyphenyl)-1-piperazine afforded 3-[[4-(2-methoxyphenyl)piperazin-1-yl]methyl]-2,3-dihydro-1*H*-imidazo[1,2-*b*][1,2,4]-benzothiadiazine 5,5-dioxide (**33a**) in 46% yield and 3-[[4-(2-methoxyphenyl)piperazin-1-yl]methyl]-2,3-dihydro-1*H*-imidazo[1,2-*b*][1,2,4]benzothiadiazine 5,5-dioxide (**35**) in 24% yield. Similarly, the elimination of hydrogen bromide from compound **30** also yielded large amounts of 3-methylene-2,3-dihydro-1*H*-imidazo[1,2-*b*]-[1,2,4]benzothiadiazine 5,5-dioxide (**35**). However, compound **35** did not undergo acid-catalyzed isomerization of the exocyclic double bond (Scheme 2).

To study the pharmacological effect of inserting a double bond between C-2 and C-3 in compounds **4** and **5**, the key intermediates 2-methylimidazo[1,2-*c*]quinazolin-5(6*H*)-one (**39**) and 3-methylimidazo[1,2-*c*]quinazolin-5(6*H*)-one (**47**) were synthesized. 2-(Bromomethyl)-5-(methylthio)imidazo[1,2-*c*]quinazoline (**38**),[9] prepared according to a previously reported procedure, was refluxed with potassium carbonate in DMF to give **39** in good yield. When **39** was treated with bromine in carbon tetrachloride at room temperature, only 2-methyl-3-bromoimidazo[1,2-*c*]quinazolin-5(6*H*)-one (**40**) was obtained in 85% yield. However, 2-(bromomethyl)-3-bromoimidazo[1,2-*c*]quinazolin-5(6*H*)-one (**41**) was obtained in 91.6% yield when **39** was treated at room temperature with NBS in the presence of AIBN in dichloroethane and carbon tetrachloride. Recrystallization of the crude product in ethanol allowed the isolation of 2-(ethoxymethyl)-3-bromoimidazo[1,2-*c*]-quinazolin-5(6*H*)-one in 40% yield. Compound **41** was subsequently treated with (2-substituted phenyl)piperazine hydrochloride in the presence of sodium bicarbonate in CH_3CN at reflux to afford 3-bromo-2-[[4-(2-substituted phenyl)piperazin-1-yl]methyl]imidazo[1,2-*c*]quinazolin-5(6*H*)-one (**42**) in good yield. The reductive debromination of **42** was performed with a catalytic amount of Pd/C under hydrogen to give 2-[[4-(2-substituted phenyl)piperazin-1-yl]methyl]imidazo[1,2-*c*]quinazolin-5(6*H*)-one (**44**). Compounds **43** and **45** were obtained in good yields by treatment of **42** and **44** with methyl iodide under basic conditions, respectively (Scheme 3).

Scheme 3[a]



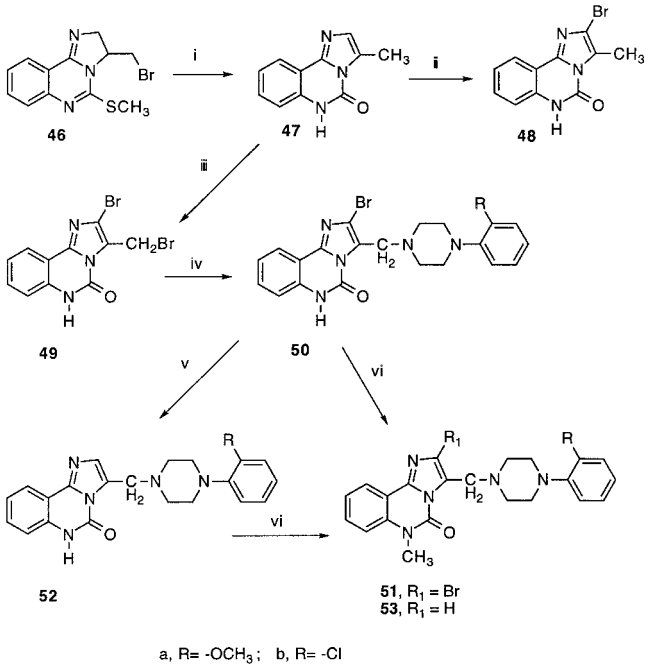
[a] (i) K_2CO_3, DMF, reflux, 88%; (ii) Br_2, CCl_4, rt, 85%; (iii) NBS, AIBN, dichloroethane/CCl_4, rt, 2 days, 91.6%; (iv) 4-substituted piperazine hydrochloride, $NaHCO_3$, CH_3CN, reflux, **42a** (59%), **42b** (44.7%); (v) H_2, Pd/C, DMF, **44a** (63%), **44b** (80%); (vi) NaH, CH_3I, DMF, rt, **45a** (61%), **45b** (56%), **43a** (65%), **43b** (52%).

2-(Bromomethyl)-3-bromo-5-(methylthio)imidazo[1,2-*c*]quinazoline (**49**) was obtained by an analogous reaction in which 2-(bromomethyl)-5-(methylthio)imidazo-[1,2-*c*]quinazoline (**46**)[9] was treated with (2-substituted phenyl)piperazine, followed by reductive debromination with Pd/C under hydrogen and subsequent methylation with methyl iodide to give compounds **50**−**53**, respectively (Scheme 4). By starting from compound **19**, compounds **54**−**56** were prepared by the same reaction sequence (Scheme 5). Compounds (*S*)-(−)-**5** and (*R*)-(+)-**5** were obtained in 94% and 98% yield by treatment of (*S*)-(+)-**57**[19] and (*R*)-(−)-**57**[19] with aqueous sodium hydroxide (Scheme 6).

Results and Discussion

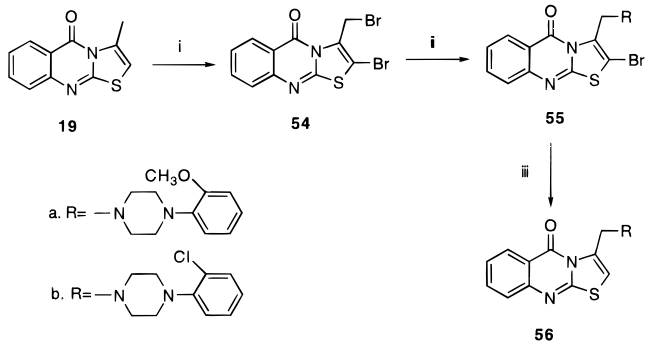
Tables 1−5 list the α_1-adrenoceptor binding affinity of various heterocycles containing a (2-substituted phe-

Scheme 4[a]



[a] (i) K_2CO_3, DMF, reflux, 67%; (ii) Br_2, CCl_4, rt, 55%; (iii) NBS, AIBN, dichloroethane/CCl_4, rt, 2 days, 90%; (iv) 4-substituted piperazine hydrochloride, $NaHCO_3$, CH_3CN, reflux, **50a** (53%), **50b** (28.7%); (v) H_2, Pd/C, DMF, **52a** (81.6%), **52b** (70%); (vi) NaH, CH_3I, DMF, rt, **51a** (57%), **51b** (50%), **53a** (72.7%), **53b** (31%).

Scheme 5[a]

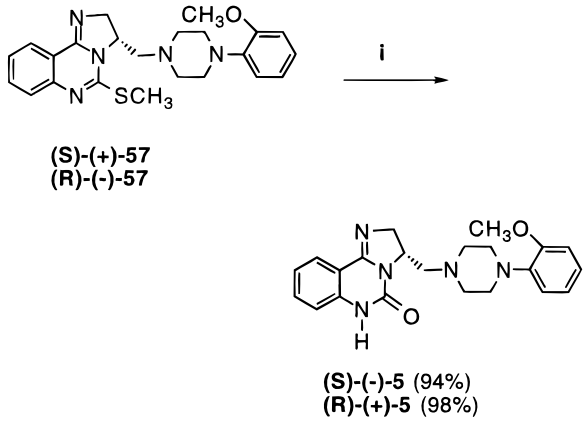


[a] (i) NBS, AIBN, dichloroethane/CCl_4, rt, 61%; (ii) 4-substituted piperazine, $NaHCO_3$, CH_3CN, reflux, **55a** (67%), **55b** (57%); (iii) H_2, Pd/C, DMF, **56a** (60%), **56b** (51%).

nyl)piperazine moiety. Some selective compounds with high affinity for the α_1-adrenoceptor were identified. The most active structural feature for receptor binding appears to be the 3-methyl-2,3-dihydroimidazo[1,2-*c*]-quinazolin-5(6*H*)-one ring system.

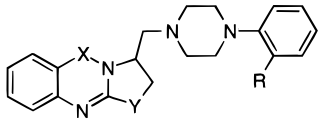
Synthesis of the constrained analogue of **1** to map the active site of the receptor led to the discovery that angular tricyclic compounds are potent and selective α_1-adrenoceptor antagonists. To further define the receptor, linear tricycles were synthesized by changing the 2,3-dihydroimidazo[1,2-*c*]quinazoline ring system to 2,3-dihydrothiazolo[2,3-*b*]quinazolin-5-one (**15a**), 2,3-dihydroimidazo[2,1-*b*]quinazolin-5-one (**16a**), and 2,3-dihydroimidazo[1,2-*b*][1,2,4]benzothiadiazine 5,5-dioxide (**33a**,**b**). The effects of attaching the phenylpiperazine side chain to different heterocycles on α_1- and α_2-adrenoceptor binding affinities are summarized in Table 1. Surprisingly, only those compounds containing a built-in guanidino moiety such as compounds **16a** and

Scheme 6[a]



[a] (i) Aq NaOH, reflux, 17 h, then HCl.

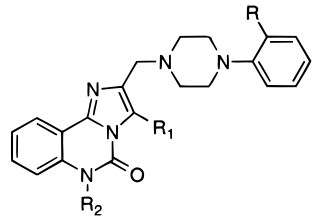
Table 1. α_1- and α_2-Adrenergic Receptor Binding Affinities for 3-[[4-(2-Substituted phenyl)piperazin-1-yl]methyl]-5*H*-2,3-dihydrothiazolo[2,3-*b*]quinazolin-5-ones



				K_i,[a] nM		
no.	X	Y	R	α_1-AR	α_2-AR	α_2/α_1
15a	C=O	S	OCH_3	>10000	ND[b]	ND
16a	C=O	NH	OCH_3	186	ND[b]	ND
33a	SO_2	NH	OCH_3	4.95 ± 0.19	460 ± 17	93
33b	SO_2	NH	Cl	11.8 ± 1.0	2290 ± 12	194

[a] The K_i binding data were calculated as described in the Experimental Section. Values are means (±SEM) of three to six separate experiments. [b] ND, not determined.

Table 2. α_1- and α_2-Adrenergic Receptor Binding Affinities for 2-[[4-(2-Substituted phenyl)piperazin-1-yl]methyl]imidazo-[1,2-*c*]quinazolin-5(6*H*)-ones

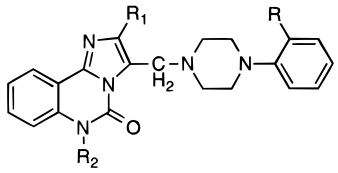


				K_i,[a] nM		
no.	R	R_1	R_2	α_1-AR	α_2-AR	α_2/α_1
42a	OCH_3	Br	H	>10000	ND[b]	ND
42b	Cl	Br	H	>10000	ND	ND
43a	OCH_3	Br	CH_3	>10000	ND	ND
43b	Cl	Br	CH_3	>10000	ND	ND
44a	OCH_3	H	H	6.53 ± 1.33	6760 ± 440	1034
44b	Cl	H	H	9.29 ± 0.94	4510	486
45a	OCH_3	H	CH_3	6.5	3250	499
45b	Cl	H	CH_3	14.1	513	36

[a] The K_i binding data were calculated as described in the Experimental Section. Values are means (±SEM) of three to six separate experiments. [b] ND, not determined.

33a,**b** antagonized the α_1-adrenoceptor. Compound **33a** was the most potent antagonist in this series with 38-fold greater potency than **16a**. When the *o*-methoxy group was replaced by *o*-chloro (**33b**), the affinity decreased 2.4-fold, in agreement with reports[8,9] showing that the introduction of these two substituents to the

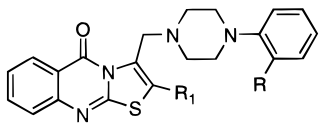
Table 3. α_1- and α_2-Adrenergic Receptor Binding Affinities for 3-[[4-(2-Substituted phenyl)piperazin-1-yl]methyl]imidazo-[1,2-*c*]quinazolin-5(6*H*)-one Derivatives



				K_i,[a] nM		
no.	R	R_1	R_2	α_1-AR	α_2-AR	α_2/α_1
50a	OCH_3	Br	H	>10000	ND[b]	ND
50b	Cl	Br	H	>10000	ND	ND
51a	OCH_3	Br	CH_3	>10000	ND	ND
51b	Cl	Br	CH_3	>10000	ND	ND
52a	OCH_3	H	H	5.06 ± 0.34	7830 ± 8.8	1550
52b	Cl	H	H	7.12 ± 1.39	2720 ± 690	382
53a	OCH_3	H	CH_3	6.1 ± 0.9	3090 ± 63	506
53b	Cl	H	CH_3	4.28 ± 0.34	525 ± 65	123

[a] The K_i binding data were calculated as described in the Experimental Section. Values are means (±SEM) of three to six separate experiments. [b] ND, not determined.

Table 4. α_1- and α_2-Adrenergic Receptor Binding Affinities for 3-[[4-(2-Substituted phenyl)piperazin-1-yl]methyl]-5*H*-thiazolo-[2,3-*b*]quinazolin-5-ones



			K_i,[a] nM		
no.	R	R_1	α_1-AR	α_2-AR	α_2/α_1
55a	OCH_3	Br	>10000	ND[b]	ND
55b	Cl	Br	>10000	ND	ND
56c	OCH_3	H	>10000	ND	ND
56d	Cl	H	>10000	ND	ND

[a] The K_i binding data were calculated as described in the Experimental Section. Values are means (±SEM) of three to six separate experiments. [b] ND, not determined.

ortho position of the phenyl ring of the phenylpiperazine side chain may produce potent α_1-adrenoceptor antagonists. Compounds **33a**,**b** also displayed lower affinity for α_2-adrenoceptors than for α_1-adrenoceptors. The α_2/α_1-selectivity ratio of **33b** was higher than that of **33a**. Compounds containing built-in pseudothiourea, such as **15a** and **32a**, were inactive for both α_1- and α_2-adrenoceptors.

Previous studies on conformational modifications of **1** found that compounds **4** and **5** were potent α_1-antagonists.[9] However, these are chiral compounds that possess an asymmetric carbon. Neither *R*- nor *S*-form enatiomers exist in an extended form as demonstrated by an initial examination simple stick−ball molecular structure model. We presumed that insertion of a double bond between the 2- and 3-positions of compounds **4** and **5** might provide improved conformations for binding to the receptor. The effects of introducing a double bond in compounds **4** and **5** on α_1- and α_2-adrenoceptor binding affinity are shown in Tables 2 and 3. Comparison of the α_1-antagonizing activity of compounds **42a** and **50a** with the corresponding parent compounds **4** and **5** illustrates that the coplanarity of compounds **42a** and **50a** did not increase receptor binding affinity. Compounds **42a**,**b**, **43a**,**b**, **50a**,**b**, and **51a**,**b** with a bromine atom at either the 3- or 2-position are key intermediates for the synthesis of the corresponding target compounds **44a**,**b**, **45a**,**b**, **52a**,**b**, and **53a**,**b**, respectively. Surprisingly, none of the intermediates was active against either α_1- or α_2-adrenoceptors. Introduction of a bromo atom into the benzene ring of the 2,3-imidazo[1,2-*c*]quinazolin-5(6*H*)-one ring system was detrimental, producing inactive compounds. However, compounds **44a**,**b** and **45a**,**b** demonstrated potent and selective affinity toward the α_1-adrenoceptor in the 6.5−14.1 nM range. Similarly, compounds **52a**,**b** and **53a**,**b** were potent and selective α_1-antagonists in the 4.28−7.12 nM range. Compound **52a** (K_i = 5.06 nM) and compound **44a** (K_i = 6.53 nM) had similar potencies, in agreement with a report[9] showing that substitution at the 3-position increased the affinity of compound **5** toward α_1-adrenoceptors more than compound **4**. There were no significant differences between the α_1-adrenoceptor binding affinities of the 6-alkylated derivatives (**45a**,**b**, **53a**,**b**) and the corresponding parent compounds (**44a**,**b**, **52a**,**b**), whereas compounds with a (2-methoxyphenyl)piperazine side chain (**44a**, **45a**, **52a**) exhibited slightly higher affinities than compounds with a (2-chlorophenyl)piperazine side chain (**44b**, **45b**, **52b**) withe the exception of compounds **53a**,**b**. All these compounds (**44a**,**b**, **45a**,**b**, **52a**,**b**, **53a**,**b**) displayed lower affinity for α_2-adrenoceptors. Most compounds displayed high α_2/α_1 ratios but were not better than the parent compound **5** with an α_2/α_1 ratio of 2823. Addition of a (2-substituted phenyl)piperazine side chain at the 3-position of the 5*H*-thiazolo[2,3-*b*]quinazolin-5-one ring system blocked α_1-adrenoceptor activity (Table 4).

To further elucidate the stereochemical requirements for pharmacological activity, the enantiomers of compounds **5** and **57** were prepared and examined in the α_1-adrenoceptor binding assay (Table 5). The affinity of enantiomer (*S*)-(+)-**57** for α_1-adrenoceptors (K_i = 1.0 ± 0.2 nM) was 144-fold greater than that of enantiomer (*R*)-(−)-**57** (K_i = 144 ± 23 nM), whereas racemic **57** had a K_i value of 0.90 ± 0.08 nM. The affinity of enantiomer (*S*)-(−)-**5** with K_i = 0.13 ± 0.01 nM was 200-fold greater than that of (*R*)-(+)-**5** (K_i = 26 ± 8 nM). The K_i value of racemic **5** was 0.21 ± 0.02 nM.

Three subtypes of the human α_1 receptor have been cloned and expressed: α_{1a}, α_{1b}, and α_{1d}.[20] The α_1-adrenoceptor has recently received much attention because the antagonist blockade of norepinephrine- or phenylephedrine-induced contraction of human prostate tissue has been found to correlate with affinity for the α_{1a} subtype.[21] Radioligand binding assays of selected compounds **4**, **5**, and **57** and their chiral compounds revealed that only compound **4** demonstrated approximately 8-fold selectivity for α1A binding sites vs α1B sites (Table 5). There were no significant difference between the α1A and α1B binding affinities of compounds (*S*)-(−)-**5** and (*S*)-(+)-**57**. Radioligand binding assays were performed essentially as reported.[23] The compounds active against the α_1 sites ((*S*)-(−)-**5** and (*S*)-(+)-**57**) were poor ligands for the α_{2a} and α2B sites.

The affinity of compounds **4**, **5**, **44a**, **52a**,**b**, and **57** and their chiral compounds for a large number of receptors was 3 orders of magnitude less than their affinity to the α_1-adrenoceptors (Table 6). Compounds with a 4-(2-methoxyphenyl)-1-piperazine side chain

Table 5. α_1- and α_2-Adrenergic Receptor Binding Affinities for Compounds **1**, **4**, **5**, and **57** and the Corresponding Chiral Compounds

	K_i,[a–c] nM						
compd	α_1-AR	α1A-AR	α1B-AR	α_2-AR	α_{2a}-AR	α2B-AR	α_2/α_1
1	0.25 ± 0.06[d]	0.5	1.1	1599 ± 324[d]	1811	56	6396
4	0.93 ± 0.13	0.65 ± 0.12	5.5 ± 0.4	230 ± 47	547 ± 63	253 ± 26	247
5	0.21 ± 0.02	0.26 ± 0.02	0.67 ± 0.05	593 ± 6	ND[e]	ND	2823
(*S*)-(−)-**5**	0.13 ± 0.01	0.23 ± 0.04	0.42 ± 0.05	183 ± 32	444 ± 89	116 ± 17	1407
(*R*)-(+)−**5**	26 ± 8	55 ± 9	123 ± 28	>10000	ND	9300 ± 1200	>384
57	0.90 ± 0.08	0.93 ± 0.04	3.9 ± 0.3	970 ± 2	ND	ND	1078
(*S*)-(+)−**57**	1.0 ± 0.2	1.5 ± 0.2	1.4 ± 0.1	3500 ± 800	872	376	3500
(*R*)-(−)-**57**	144 ± 23	122 ± 15	667 ± 20	9000 ± 1500	3000	ND	62.5

[a] The K_i binding data were calculated as described in the Experimental Section. Values are means (±SEM) of three to six separate experiments. [b] The following radioligands were used: [^{3}H]prazosin for α_1, α1A, and α1B assays; [^{3}H]clonidine for α_2 assays; [^{3}H]MK912 for α_{2a} assays; [^{3}H]yohimbine for α2B assays. [c] Radioligand studies against α1A, α1B, α_{2a}, and α2B sites were performed by Pan Lab, Inc.[22] [d] Data were taken from ref 9. [e] ND, not determined.

Table 6. Affinity of Compounds **1**, **4**, **5**, **44a**, **52a**,**b**, and **57** for Different Receptors

			K_i,[a] nM						
assay	ligand	source	**1**	**4**	**5**	**44a**	**52a**	**52b**	**57**
5-HT$_1$	[^{3}H]-5-HT	rat brain cortex	1510	2500	—[b]	—	—	—	1839
5-HT$_{1A}$	[^{3}H]-8-OH-DPAT	rat brain cortex	16	238	155	—	4000	—	237
5-HT$_2$	[^{3}H]ketanserin	rat brain	180	369	377	3580	514	114	168
σ	[^{3}H]pentazocine	guinea pig brain	—	4000	6270	743	6520	1500	451
σ 2	[^{3}H]ifenprodil	rat brain	—	—	—	4880	—	3050	—
D$_2$	[^{3}H]spiperone	CHO cells	32	—	158	—	—	—	449
rhD$_2$	[^{3}H]spiperone	CHO cells	132	—	239	—	—	—	—
rhD$_3$	[^{3}H]spiperone	CHO cells	73	2200	985	—	—	—	—
H$_1$	[^{3}H]pyrilamine	guinea pig lung	685	961	2320	—	—	—	—
sodium channel	[^{3}H]batrachotoxin	rat brain	3680	—	—	4810	5380	2460	404

[a] Inhibition constants (K_i) for in vitro inhibition by the compounds were studied by Pan Lab, Inc.[22] [b] A dash (−) indicates that the inhibition percentage was below 50% at the concentration of 10 μM for each compound.

were reported to be potent 5-HT1A agents.[11] Compounds **4**, **5**, and **57**, which are the most potent α_1-AR binders, were also ligands for the 5-HT1A receptor with K_i = 238, 155, and 237 nM, respectively. However, the insertion of a double bond into compounds **4** and **5** between positions 2 and 3 (compounds **44a**, **52a**,**b**) decreased or totally abrogated binding to the 5-HT1A receptor and D$_2$ site. However, compound **1** was not only a potent α_1-AR antagonist but also a potent ligand for 5-HT$_{1A}$ (K_i = 16 nM) and D$_2$ (K_i = 32 nM), although it was a weak ligand at H$_1$ (K_i = 685 nM). It should be noted that compound **57** was also a weak ligand for the sodium channel with K_i = 404 nM.

Compounds (*S*)-(−)-**5** and (*R*)-(+)-**5** were evaluated for blood pressure-lowering activity in anesthetized spontaneously hypertensive rats (SHR) by intravenous administration (Figure 1A,B). Administration of (*S*)-(−)-**5** (0.005, 0.01, and 0.05 mg/kg, iv bolus) and (*R*)-(+)-**5** (0.05, 0.1, and 0.2 mg/kg, iv bolus) produced a dose-dependent reduction of mean arterial pressure (MAP) which reached a maximal effect after 5 min and persisted for over 3 h (Figure 1). (*S*)-(−)-**5** was approximately 3-fold more potent than (*R*)-(+)-**5** based on the peak effect at the same dose. Neither (*S*)-(−)-**5** nor (*R*)-(+)-**5** significantly affected the heart rate (Figure 2).

In summary, this investigation demonstrated that the *S*-forms of 3-substituted 2,3-dihydroimidazo[1,2-*c*]-quinazoline derivatives are more active than the *R*-forms for antagonism of the α_1-adrenoceptor. The *S*-form might provide a better conformational fit to the α_1-adrenoceptor.

Experimental Section

Chemistry. General Methods. Melting points were obtained on an Electrothermal apparatus and are uncorrected. ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on either a JEOL FX-100 or a JEOL JNM-EX400 spectrometer at the National Taiwan Normal University or on a Bruker model AM 300 spectrometer at the National Taiwan University, Taipei, and are reported in parts per million with DMSO-d_6 as internal standard on a δ scale. EI mass spectra were recorded on a JEOL JMS-D100 mass spectrometer at the National Taiwan University. Elemental analyses for C, H, and N were carried out either on a Heraeus elemental analyzer in the Cheng-Kong University, Tainan, or on a Perkin-Elmer 240 elemental analyzer in the National Taiwan University, Taipei, and were within ±0.4% of the theoretical values.

3-(Methylsulfinyl)quinazolin-4(3*H*)-one (10). To a mixture of **9** (2.0 g, 10.4 mmol) in chloroform (50 mL) was added dropwise 60% 3-chloroperoxybenzoic acid (4.0 g, 23.2 mmol) in chloroform (10 mL) under ice bath. After the mixture was stirred at room temperature for 1 h, to the mixture was added saturated sodium bicarbonate solution (50 mL). The organic layer was collected and evaporated to dryness. The solid was collected and recrystallized from water to furnish **10** (1.82 g, 85%): mp 144 °C dec; ^{1}H NMR (100 MHz, DMSO-d_6) δ 2.99 (s, 3 H, CH_3), 7.50−7.95 (m, 3 H, Ar−H), 8.14 (d, 1 H, J = 8.6 Hz, Ar−H), 12.13 (br, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 121.9, 126.3, 127.9, 135.0, 146.8, 160.0, 161.2; MS *m*/*z* 208 (M^+), 192 ($M^+ - 16$), 177 ($M^+ - 31$). Anal. ($C_9H_8N_2O_2S_2$) C, H, N.

2-(Allylthio)quinazolin-4(3*H*)-one (11). To a solution of **8** (3.0 g, 16.85 mmol) and sodium hydroxide (0.67 g, 16.9 mmol) in water (150 mL) was added allyl bromide (1.5 mL, 17.36 mmol). The mixture was stirred at room temperature for 30 min before being neutralized with acetic acid to give a white solid which was collected by filtration and recrystallized from ethanol and water (9:1) to afford **11** (3.6 g, 98%): mp 184 °C dec; ^{1}H NMR (100 MHz, DMSO-d_6) δ 3.87 (d, 2 H, J = 7.7 Hz, CH_2), 5.07−5.42 (m, 2 H, CH_2), 5.84−6.01 (m, 1H, CH), 7.31−7.55 (m, 2 H, Ar−H), 7.66−7.82 (m, 1 H, Ar−H), 7.97−8.05 (m, 1 H, Ar−H), 12.43 (br s, 1 H, NH); ^{13}C NMR (25 MHz, DMSO-d_6) δ 32.3, 118.4, 119.8, 125.5, 125.7, 125.80, 133.1, 134.4, 148.0, 154.8, 161.0; MS *m*/*z* 218 (M^+). Anal. ($C_{11}H_{10}N_2OS$) C, H, N.

2-(Allylamino)quinazolin-4(3*H*)-one (12). To a mixture of **10** (0.96 g, 4.42 mmol) and sodium bicarbonate (1.2 g, 8.84

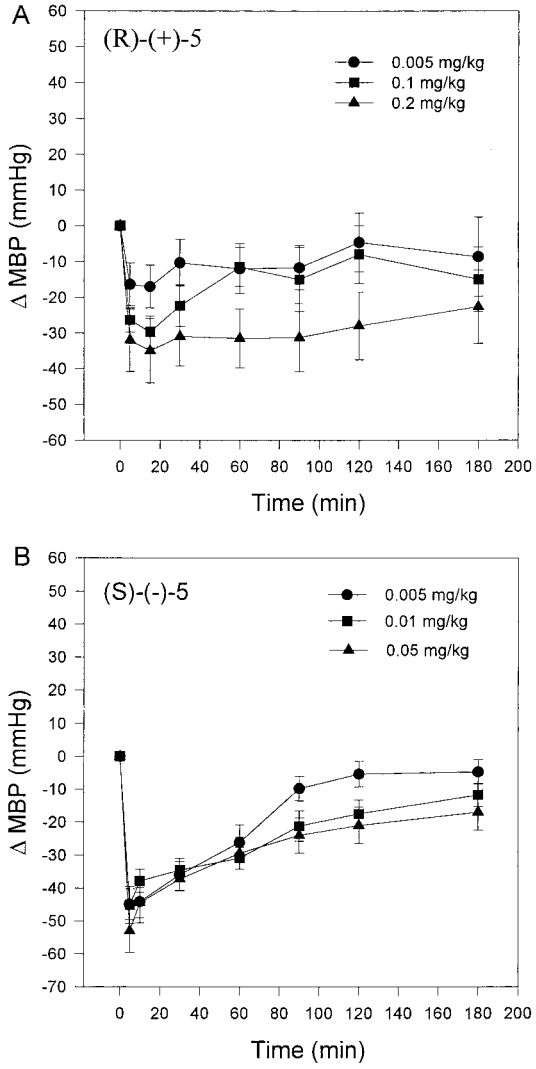


Figure 1. Time course of the depressor effect of (*R*)-(+)-**5** (A) and (*S*)-(−)-**5** (B) on spontaneously hypertensive rats.

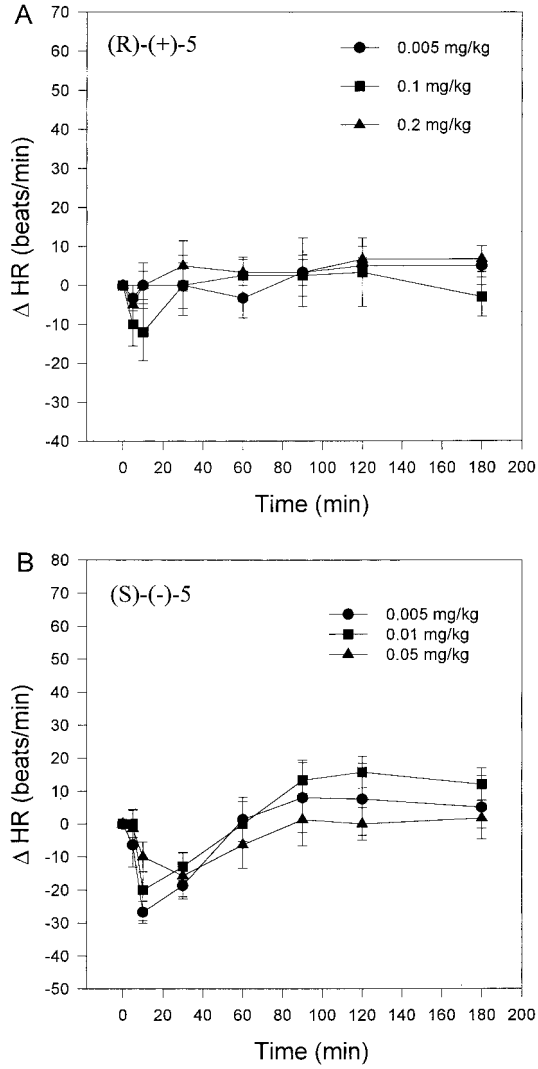


Figure 2. Time course of heart rate changes after an intravenously administered series of doses of (*R*)-(+)-**5** (A) and (*S*)-(−)-**5** (B) on spontaneously hypertensive rats.

mmol) in acetonitrile (20 mL) was added allylamine hydrochloride (0.65 g, 6.95 mmol). The mixture was refluxed for 1 h, and the hot mixture was then vacuum-filtered to remove solids. The filtrate was cooled to room temperature, and the precipitate was collected by filtration to afford crystals. The solid was recrystallized from a mixture of DMF and water (3:1) to furnish **12** (0.69 g, 78%): mp 185 °C dec; ^{1}H NMR (100 MHz, DMSO-d_6) δ 3.99 (t, 2 H, CH_2), 5.05−5.31 (m, 2 H, $=CH_2$), 5.77−6.10 (m, 1 H, CH), 7.03 (br s, 1 H, NH), 7.04−7.26 (m, 2 H, Ar−H), 7.44−7.56 (m, 1 H, Ar−H), 7.86−7.93 (m, 1 H, Ar−H), 11.06 (br s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 42.3, 115.3, 117.4, 121.6, 125.9, 126.9, 134.0, 134.8, 135.1, 140.8, 150.6; MS *m*/*z* 200 (M^+). Anal. ($C_{11}H_{10}N_3O\cdot {}^1/_2H_2O$) C, H, N.

3-(Bromomethyl)-2,3-dihydro-5*H*-thiazolo[2,3-*b*]-quinazolin-5-one (13). A solution of **11** (2.9 g, 13.3 mmol) and NBS (2.4 g, 13.48 mmol) in THF was stirred at room temperature for 30 min. The mixture was then concentrated in vacuo to dryness. To the resulting residue was added water (5 mL), and the solid was then collected by filtration to give 4.1 g of the crude product which was recrystallized from ethanol to furnish **13** (3.8 g, 96%): mp 235−237 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.50−3.83 (m, 2 H, CH_2), 3.91−4.01 (m, 2 H, CH_2), 5.72 (t, 1 H, J = 6.5 Hz, CH), 7.45 (t, 1 H, J = 7.6 Hz, Ar−H), 7.59 (d, 1 H, J = 6.0 Hz, Ar−H), 7.79 (t, 1 H, J = 7.8 Hz, Ar−H), 8.02 (d, 1 H, J = 7.7 Hz, Ar−H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 30.2, 32.0, 61.2, 115.9, 117.5, 125.5, 127.8, 134.2, 138.0, 166.0, 168.6; MS *m*/*z* 297 (M^+), 217 (M^+ − 80). Anal. ($C_{11}H_9N_2BrOS$) C, H, N.

3-(Bromomethyl)-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one (14). A solution of **12** (0.6 g, 3.14 mmol) and NBS (0.7 g, 3.9 mmol) in THF (20 mL) was stirred at room temperature for 30 min. The solvent was removed in vacuo to dryness. To the residue was added water (10 mL), and the solid was then collected by filtration. The crude product was recrystallized from DMF and methanol (3:1) to furnish **14** (0.8 g, 93%): mp 235−237 °C; ^{1}H NMR (100 MHz, DMSO-d_6) δ 3.48−3.60 (m, 2 H, CH_2), 3.78−4.02 (m, 2 H, CH_2), 5.13−5.25 (m, 1 H, CH), 7.15−7.38 (m, 2 H, Ar−H), 7.54−7.70 (m, 1 H, Ar−H), 7.89−7.97 (m, 1 H, Ar−H), 8.24 (br s, 1 H, NH); ^{13}C NMR (25 MHz, DMSO-d_6) δ 35.0, 44.8, 55.1, 113.0, 117.3, 122.5, 127.6, 132.8, 138.0, 158.2, 168.1; MS *m*/*z* 280 (M^+), 200 (M^+ − 80). Anal. ($C_{11}H_{10}N_3BrO$) C, H, N.

3-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (15a) and 3-Methylene-2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (17). These were prepared by a similar approach which afforded **16a**. Compound **15**: R_f = 0.62, chloroform/ethyl acetate = 9/1; yield 16%, mp 261−264 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.49−2.58 (m, 6 H, 3 CH_2), 2.73−2.95 (m, 6 H, 3 CH_2), 3.76 (s, 3 H, CH_3), 5.49 (m, 1 H, CH), 6.86−6.92 (m, 4 H, Ar−H), 7.42−7.54 (m, 2 H, Ar−H), 7.79−8.04 (m, 2 H, Ar−H); MS *m*/*z* 408 (M^+). Anal. ($C_{22}H_{24}N_4SO_2$) C, H, N.

Compound **17**: R_f = 0.66, chloroform/ethyl acetate = 9/1; yield 70%, mp 205 °C dec; ^{1}H NMR (100 MHz, DMSO-d_6) δ 4.24 (s, 2 H, CH_2), 5.38 (s, 1 H, =C−H), 5.57 (s, 1 H, =C−H), 7.58−8.07 (m, 4 H, Ar−H); ^{13}C NMR (25 MHz, DMSO-d_6) δ

32.5, 101.5, 116.3, 117.9, 125.8, 127.9, 133.6, 137.3, 141.2, 168.0, 169.6; MS *m/z* 216 (M^+). Anal. ($C_{11}H_8N_2OS$) C, H, N.

3-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one (16a). A suspension of **14** (0.5 g, 1.78 mmol), (2-methoxyphenyl)piperazine hydrochloride (0.82 g, 3.57 mmol), and sodium hydrocarbonate (0.3 g, 3.57 mmol) in acetonitrile (70 mL) was refluxed for 2 days. The white solid was then collected by filtration and recrystallized from DMF to give **16a** (0.5 g, 50%): mp 293−294 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.55−2.96 (m, 10 H, 5 CH_2), 3.60−3.79 (m, 2 H, CH_2), 3.76 (s, 3 H, $-OCH_3$), 4.96 (m, 1H, CH), 6.85−6.92 (m, 4 H, Ar−H), 7.18−7.30 (m, 2 H, Ar−H), 7.62−7.64 (m, 1 H, Ar−H), 7.90−7.93 (m, 1 H, Ar−H), 8.17 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 44.4, 50.0, 53.5, 53.8, 55.3, 57.6, 111.9, 113.6, 117.4, 117.9, 120.8, 122.3, 127.6, 132.8, 138.3, 141.1, 151.9, 158.5, 168.8. Anal. ($C_{22}H_{25}N_5O_2$) C, H, N.

The mother liquid was subjected to column chromatography (silica gel, 15 g; solvent system, $CHCl_3$/MeOH = 95/5), and the R_f = 0.22 fraction was collected and concentrated in vacuo to give **18** (30 mg, 8.4%): mp >300 °C (ethanol); ^{1}H NMR (300 MHz, DMSO-d_6) 4.35 (s, 2 H, CH_2), 4.83 (d, 1 H, J = 2.5 Hz, =C−H), 5.46 (d, 1 H, J = 2.9 Hz, =C−H), 7.32−8.01 (m, 4 H, Ar−H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 29.4, 40.7, 46.4, 50.4, 92.0, 114.7, 124.3, 128.4, 133.7, 137.5, 140.5; MS *m/z* 198 ($M^+ - 1$). Anal. ($C_{11}H_9N_3O$) C, H, N.

3-Methylene-2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (17). A mixture of **13** (2.1 g, 7.1 mmol) and potassium carbonate (2.0 g, 14.5 mmol) in methyl isobutyl ketone (30 mL) was refluxed for 1 h. The solid was filtered off, and the filtrate was cooled to room temperature. The crystal needles were collected by filtration to furnish **17** (1.43 g, 88%), mp 203−204 °C. The analytical data was in agreement with the above data.

3-Methyl-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (19). A mixture of **17** (0.75 g, 3.45 mmol) in concentrated sulfuric acid (10 mL) was heated at 45 °C for 20 min. The solution was then neutralized with 10% sodium hydroxide solution to pH 7. The white solid was collected and recrystallized from ethanol to afford **19** (0.73 g, 98%): mp >300 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.84 (s, 3 H, CH_3), 7.02 (s, 1 H, =C−H), 7.60−7.65 (m, 2 H, Ar−H), 7.80−7.86 (m, 2 H, Ar−H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 19.4, 105.5, 116.9, 124.2, 125.2, 126.9, 128.2, 132.92, 133.7, 134.6, 168.2; MS *m/z* 216 (M^+). Anal. ($C_{11}H_8N_2OS$) C, H, N.

1,2,4-Benzothiadiazine-3(4*H*)-thione (22). To a mixture of 2-aminobenzenesulfonamide (4.5 g, 29 mmol) in ethanol (50 mL) were added sodium hydrocarbonate (4.0 g, 48 mmol) in water (10 mL) and carbon disulfide (15 mL, 0.25 mol). The mixture was refluxed for 24 h, cooled to room temperature, and neutralized with acetic acid to pH 6.5. The white solid was then collected by filtration and recrystallized from ethanol to give **22** (6.6 g, 94%).

3-(Methylthio)-4*H*-1,2,4-benzothiadiazine 1,1-Dioxide (23). This was prepared in 99% yield by a similar approach which afforded **9**. An analytical sample was recrystallized from water: mp 220 °C dec; ^{1}H NMR (100 MHz, DMSO-d_6) δ 2.53 (s, 3 H, CH_3), 7.10−7.80 (m, 4 H, Ar−H), 12.30 (br s, 1 H, NH); ^{13}C NMR (25 MHz, DMSO-d_6) δ 13.4, 116.7, 121.5, 123.2, 125.8, 133.1, 135.4, 160.7; MS *m/z* 228 (M^+). Anal. ($C_8H_8N_2O_2S_2$) C, H, N.

3-(Methylsulfinyl)-4*H*-1,2,4-benzothiadiazine 1,1-Dioxide (24). To a solution of **23** (0.5 g, 2.2 mmol) in acetic acid (20 mL) was added 30% hydrogen peroxide (2 mL). The mixture was stirred at room temperature for 24 h, and the white solid was then collected by filtration. The crude product was recrystallized from ethanol to give **24** (0.42 g, 79%): mp 267−268 °C; ^{1}H NMR (100 MHz, DMSO-d_6) δ 2.99 (s, 3 H, CH_3), 7.66−8.18 (m, 4 H, Ar−H), 12.52 (br s, 1 H, NH); ^{13}C NMR (25 MHz, DMSO-d_6) δ 121.7, 126.1, 126.9, 127.7, 134.8, 146.6, 159.7, 160.9; MS *m/z* 244 (M^+), 228 ($M^+ - 16$), 213 ($M^+ - 31$). Anal. ($C_8H_8N_2O_3S_2$) C, H, N.

3-(Allylthio)-4*H*-1,2,4-benzothiadiazine 1,1-Dioxide (25). To a solution of **22** (2.0 g, 9.35 mmol) and sodium hydroxide in water was added allyl bromide (0.9 mL, 10 mmol). The mixture was stirred at room temperature for 20 min. The solid was collected by filtration and recrystallized from water to furnish **25** (2.2 g, 93%): mp 135−136 °C; ^{1}H NMR (100 MHz, DMSO-d_6) δ 3.34 (t, 2 H, J = 5.0 Hz, CH_2), 5.10−5.29 (m, 2 H, CH_2), 5.80 (m, 1 H, CH), 7.20−7.70 (m, 4 H, Ar−H), 10.61 (br s, 1 H, NH); ^{13}C NMR (25 MHz, DMSO-d_6) δ 32.3, 115.7, 116.4, 122.5, 125.5, 132.2, 133.1, 148.0, 154.8, 161.0; MS *m/z* 254 (M^+). Anal. ($C_{10}H_{10}N_2S_2O_2$) C, H, N.

2-(3-Allylthioureido)benzenesulfonamide (26). To a solution of 2-aminobenzenesulfonamide (**21**; 5.0 g, 29 mmol) in 2-propanol (50 mL) was added allyl isothiocyanate (4 mL, 41 mmol). The mixture was stirred at room temperature for 48 h. The white solid was collected by filtration and recrystallized from ethanol to furnish compound **26** (6.3 g, 80%): mp 133−134 °C; ^{1}H NMR (100 MHz, DMSO-d_6) δ 4.16 (t, 2 H, CH_2), 5.09−5.30 (m, 2 H, $=CH_2$), 5.74−6.08 (m, 1 H, CH), 7.29−7.84 (m, 6 H, Ar−H and NH), 8.28 (s, 1 H, NH, D_2O exchangeable), 8.70 (t, 1 H, NH, D_2O exchangeable); ^{13}C NMR (25 MHz, DMSO-d_6) δ 46.6, 116.0, 124.4, 127.1, 128.2, 131.6, 134.1, 134.4, 136.7, 180.9; MS *m/z* 271 (M^+). Anal. ($C_{10}H_{13}N_3O_2S_2$) C, H, N.

3-(Allylamino)-4*H*-1,2,4-benzothiadiazine 1,1-Dioxide (27). Method A: A mixture of **26** (0.8 g, 2.95 mmol) and sodium hydrocarbonate (0.3 g, 3.57 mmol) in methanol (15 mL) was refluxed for 24 h. The mixture was cooled to room temperature, and the white solid was collected by filtration. The solid was suspended in water (20 mL) and neutralized with acetic acid (0.32 g, 51%). The filtrate was concentrated in vacuo to an oily residue. To the residue was added water (10 mL), and the whole was neutralized with acetic acid to pH 7. The resulting white solid was collected by filtration and recrystallized from water to give **27** (0.3 g, 43%): mp 151−152 °C; ^{1}H NMR (100 MHz, DMSO-d_6) δ 3.87 (t, 2 H, J = 5.0 Hz, CH_2), 5.09−5.29 (m, 2 H, CH_2), 5.74−6.08 (m, 1 H, CH), 7.17−7.31 (m, 2 H, Ar−H), 7.46−7.62 (m, 2 H, Ar−H), 10.61 (br s, 1 H, NH, D_2O exchangeable); ^{13}C NMR (25 MHz, DMSO-d_6) δ 42.7, 115.6, 116.4, 122.5, 122.7, 123.6, 132.2, 134.4, 135.5, 150.9; MS *m/z* 237 (M^+). Anal. ($C_{10}H_{11}N_3O_2S$) C, H, N.

Method B: A mixture of **24** (1.0 g, 3.85 mmol), allylamine hydrochloride, and potassium carbonate (0.8 g, 5.79 mmol) in acetonitrile (50 mL) was refluxed for 1 h. The solvent was then removed in vacuo to dryness. To the residue was added water (20 mL), and the whole was neutralized with acetic acid to pH 7. The white solid was collected by filtration and recrystallized from water to afford **27** (0.86 g, 94%), mp 150−151 °C. The analyical data was in agreement with that described above.

3-(Bromomethyl)-2,3-dihydrothiazolo[3,2-*b*][1,2,4]-benzothiadiazine 5,5-Dioxide (28). To a mixture of **25** (1.0 g, 3.9 mmol) in THF (20 mL) was added NBS (0.7 g, 4.0 mmol). The mixture was stirred at room temperature for 30 min, and the solvent was then removed in vacuo at 60 °C. The oily residue was mixed with water (20 mL) to produce a solid which was collected by filtration. The crude product was recrystallized from methanol and water (1:1) to furnish **28** (0.92 g, 71%): mp 151−152 °C; ^{1}H NMR (100 MHz, DMSO-d_6) δ 3.45−3.56 (m, 2 H, CH_2), 3.77−4.05 (m, 2 H, CH_2), 5.61−5.81 (m, 1 H, CH), 7.45−7.92 (m, 4 H, Ar−H); ^{13}C NMR (25 MHz, DMSO-d_6) δ 31.3, 34.4, 59.0, 121.4, 124.4, 126.3, 126.4, 134.6, 142.3, 160.7; MS *m/z* 333 (M^+), 253 ($M^+ - 80$), 239 ($M^+ - 94$). Anal. ($C_{10}H_9N_2BrS_2O_2$) C, H, N.

3-(Bromomethyl)-2,3-dihydro-1*H*-imidazo[1,2-*b*][1,2,4]-benzothiadiazine 5,5-Dioxide (30). To a mixture of **27** (0.63 g, 2.67 mmol) in THF was added NBS (0.5 g, 2.8 mmol). The mixture was stirred at room temperature, and the solvent was then removed in vacuo. The oily residue was mixed with CH_3-CN (20 mL) to form a solid which was collected by filtration and recrystallized from methanol to furnish **30** (0.16 g, 72%): mp 271−273 °C; ^{1}H NMR (100 MHz, DMSO-d_6) δ 3.63 (m, 2 H, CH_2), 3.86 (m, 2 H, CH_2), 5.06 (m, 1 H, CH), 7.19 (t, 2 H, J = 7.1 Hz, Ar−H), 7.52−7.81 (m, 2 H, Ar−H), 8.14 (br s, 1 H, NH); ^{13}C NMR (25 MHz, DMSO-d_6) δ 35.9, 44.1, 53.7, 121.4,

122.1, 123.2, 124.6, 134.2, 145.4, 153.5; MS *m/z* 316 (M^+), 236 ($M^+ - 80$). Anal. ($C_{10}H_{10}N_3BrO_2S$) C, H, N.

3-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-2,3-dihydro-1*H*-imidazo[1,2-*b*][1,2,4]benzothiadiazine 5,5-Dioxide (33a) and 3-Methylene-2,3-dihydro-1*H*-imidazo[1,2-*b*][1,2,4]benzothiadiazine 5,5-Dioxide (35). Compound **33a** was prepared in 46% yield using a procedure similar to that which afforded **16a**. An analytical sample was recrystallized from DMF and ethanol: mp 232−233 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.50−2.56 (m, 4 H, 2 CH_2), 2.68−2.78 (m, 2 H, CH_2), 2.93 (br s, 4 H, 2 CH_2), 3.46 (t, 1 H, J = 6.8 Hz, Ar−H), 3.76 (s, 3 H, −OCH_3), 3.79 (t, 1 H, J = 9.3 Hz, Ar−H), 4.82 (m, 1 H, CH), 6.86−6.95 (m, 4 H, Ar−H), 7.14−7.20 (m, 2 H, Ar−H), 7.58 (t, 1 H, J = 7.0 Hz, Ar−H), 7.76 (d, 1 H, J = 7.9 Hz, Ar−H), 8.29 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 44.0, 50.0, 53.2, 53.6, 55.3, 60.3, 111.9, 117.9, 120.8, 121.6, 122.0, 122.4, 123.4, 124.7, 134.2, 141.1, 146.1, 151.9, 154.1; MS *m/z* 427 (M^+). Anal. ($C_{21}H_{25}N_5O_3S$) C, H, N.

Compound **35**: 24% yield, mp 252 °C dec; ^{1}H NMR (200 MHz, DMSO-d_6) δ 4.26 (s, 2 H, CH_2), 4.85 (s, 1 H, =C−H), 5.30 (s, 1 H, =C−H), 7.22 (t, 2 H, J = 8 Hz, Ar−H), 7.62 (t, 1 H, J = 8 Hz, Ar−H), 7.83 (d, 1 H, J = 8 Hz, Ar−H), 8.60 (br s, 1 H, NH); MS *m/z* 235 (M^+). Anal. ($C_9H_9N_3O_2S$) C, H, N.

3-[[4-(2-Chlorophenyl)piperazin-1-yl]methyl]-2,3-dihydro-1*H*-imidazo[1,2-*b*][1,2,4]benzothiadiazine 5,5-Dioxide (33b). Compound **33b** was prepared in 50% yield using a procedure similar to that which afforded **16a**. An analytical sample was recrystallized from DMF and water: mp 225−226 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.52−2.93 (m, 6 H, 3 CH_2), 2.96 (br s, 4 H, 2 CH_2), 3.43−3.49 (m, 1 H, −CH−), 3.80 (t, 1 H, J = 9.2 Hz, −CH−), 4.82−4.86 (m, 1 H, −CH−), 7.00−7.05 (dt, 1 H, J = 1.5, 8.3 Hz, Ar−H), 7.13−7.20 (m, 3 H, Ar−H), 7.25−7.31 (dt, 1 H, J = 1.5, 8.5 Hz, Ar−H), 8.38−7.40 (dd, 1 H, J = 1.4, 7.9 Hz, Ar−H), 7.58 (t, 1 H, J = 6.9 Hz, Ar−H), 7.78 (d, 1 H, J = 7.83 Hz, Ar−H), 8.32 (br s, 1 H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6) δ 44.4, 51.1, 53.4, 53.8, 60.6, 121.2, 122.0, 122.5, 123.7, 124.3, 125.1, 128.0, 128.5, 130.7, 134.6, 146.2, 149.3, 154.5; MS *m/z* 431 (M^+, 70%), 432 ($M^+ + 1$), 433 ($M^+ + 2$), 434 ($M^+ + 3$), 209 ($M^+ - 222$, 100%). Anal. ($C_{20}H_{22}N_5SO_2Cl$) C, H, N.

3-Methylene-2,3-dihydrothiazolo[3,2-*b*][1,2,4]benzothiadiazine 5,5-Dioxide (34). This was prepared in 93% yield by a similar approach which afforded compound **17**. An analytical sample was recrystallized from methanol: mp 194−195 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.28 (s, 2 H, CH_2), 5.14 (s, 1 H, =CH), 5.50 (s, 1 H, =CH), 7.48 (d, 1 H, J = 8.3 Hz, Ar−H), 7.54 (t, 1 H, J = 7.3 Hz, Ar−H), 7.81 (t, 1 H, J = 8.3 Hz, Ar−H), 8.03 (d, 1 H, J = 7.3 Hz, Ar−H); ^{13}C NMR (100.4 MHz, DMSO-d_6) δ 31.2, 99.3, 122.2, 124.3, 126.5, 126.9, 135.3, 138.7, 141.7, 159.0; MS *m/z* 252 (M^+). Anal. ($C_{10}H_8N_2O_2S_2$) C, H, N.

3-Methylthiazolo[3,2-*b*][1,2,4]benzothiadiazine 5,5-Dioxide (36). Compound **36** was prepared in 90% yield using a procedure similar to that which afforded **19**: mp 179−180 °C; ^{1}H NMR (100 MHz, DMSO-d_6) δ 2.85 (s, 3 H, CH_3), 7.03 (s, 1 H, =CH), 7.53−7.89 (m, 2 H, Ar−H), 8.19−8.35 (m, 2 H, Ar−H); ^{13}C NMR (25 MHz, DMSO-d_6) δ 17.8, 105.4, 119.5, 123.8, 124.2, 128.3, 132.4, 133.6, 135.0, 167.9; MS *m/z* 252 (M^+). Anal. ($C_{10}H_8N_2O_2S_2$) C, H, N.

2-Methylimidazo[1,2-*c*]quinazolin-5(6*H*)-one (39). A mixture of **38** (6.24 g, 22.3 mmol) and potassium carbonate (7.7 g, 0.06 mol) in DMF (100 mL) was heated at 90 °C for 2 h. The solid was removed by filtration, and the filtrate was rotatory-evaporated to dryness. The residue was purified by column chromatography (silica gel, 4.6 × 20 cm, 70−230 mesh; solvent system, *n*-hexane/EtOAc/EtOH = 2:7:1). The desired fraction (R_f = 0.61) was collected, and the solvent was then removed in vacuo. The solid was recrystallized from ethanol to give **39** (3.92 g, 88%): mp 273−274 °C; ^{1}H NMR (100 MHz, DMSO-d_6) δ 2.31 (s, 3 H, CH_3), 7.19−7.57 (m, 4 H, Ar−H), 8.05 (d, 1 H, J = 7.8 Hz, Ar−H), 11.89 (s, 1 H, NH); ^{13}C NMR (25 MHz, DMSO-d_6) δ 13.8, 109.7, 111.9, 115.6, 122.4, 123.1, 129.9, 134.8, 140.5, 142.4, 144.5; MS *m/z* 199 (M^+). Anal. ($C_{11}H_9N_3O$) C, H, N.

2-Methyl-3-bromoimidazo[1,2-*c*]quinazolin-5(6*H*)-one (40). To a suspension of **39** (0.6 g, 3.01 mmol) in carbon tetrachloride (30 mL) was dropwise added bromine (0.3 mL, 5.92 mmol). The mixture was stirred at room temperature for 24 h. The solvent was then removed in vacuo, and to the residue was added acetone (20 mL). The solvent was then removed by rotavaporatoration to get a white solid which was recrystallized from CH_3CN to yield **40** (0.71 g, 85%): mp 253−255 °C; ^{1}H NMR (100 MHz, DMSO-d_6) δ 2.58 (s, 3 H, CH_3), 7.27−7.68 (m, 3 H, Ar−H), 8.09 (d, 1 H, J = 8.4 Hz, Ar−H), 11.84 (s, 1 H, NH); ^{13}C NMR (25 MHz, DMSO-d_6) δ 11.4, 111.5, 115.4, 118.8, 122.3, 123.2, 130.3, 145.3; MS *m/z* 278 (M^+). Anal. ($C_{11}H_8N_3BrO$) C, H, N.

2-(Bromomethyl)-3-bromoimidazo[1,2-*c*]quinazolin-5(6*H*)-one (41). To a suspension of **39** (2.1 g, 10.3 mmol) in a mixture of dichloroethane and carbon tetrachloride (2:1, 60 mL) were added AIBN (3.4 g, 20.68 mmol) and NBS (3.68 g, 20.68 mmol). The resulting mixture was stirred at room temperature for 2 days. The solid was collected by filtration and dried at 60 °C for 24 h. The crude product was purified by column chromatography (silica gel, 4.1 × 22.3 cm, 70−230 mesh; solvent system, $CHCl_3$/MeOH = 97:3). The desired portion (R_f = 0.56, solvent system, $CHCl_3$/MeOH = 97:3) was collected, and the solvent was then removed in vacuo. The residue was recrystallized from DMF and acetonitrile to give 3.38 g of **41** in 91.6% yield: mp 236 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.67 (s, 2 H, CH_2), 7.29 (t, 2 H, J = 6.6 Hz, Ar−H), 7.54 (t, 1 H, J = 7.8 Hz, Ar−H), 8.06 (d, 1 H, J = 7.2 Hz, Ar−H), 11.98 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 26.1, 98.9, 112.3, 116.0, 123.0, 123.8, 131.5, 135.7, 140.3, 145.1, 145.2; MS *m/z* 407 (M^+). Anal. HREIMS (exact mass HREMS) calcd for $C_{11}H_7ON_3Br_2$ *m/e* 354.8956, found 354.8956.

2-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-3-bromoimidazo[1,2-*c*]quinazolin-5(6*H*)-one (42a). To a suspension of **41** (1.0 g, 2.8 mmol) in acetonitrile (50 mL) were added 1-(2-methoxyphenyl)piperazine hydrochloride (0.83 g, 5.36 mmol) and sodium bicarbonate (1.0 g, 11.1 mol). The mixture was refluxed for 24 h. The solid was the collected, and filtrate was moved to the refrigerator. The resulting precipitate was collected, and the combined crude product was purified by column chromatography (silica gel, 2.3 × 22.5 cm, 70−230 mesh; solvent system, $CHCl_3$/CH_3OH = 98:2). The desired portion (R_f = 0.3, solvent system, $CHCl_3$/CH_3OH = 98:2) was collected, and the solvent was removed in vacuo. The residue was recrystallized from methanol with a small amount of chloroform to give 0.74 g of **42a** in 59% yield: mp 230 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.64 (s, 4 H, 2 CH_2), 2.90 (s, 4 H, 2 CH_2), 3.75 (s, 3 H, OCH_3), 4.01 (s, 2 H, CH_2), 6.88 (m, 4 H, Ar−H), 7.28−7.35 (m, 2 H, Ar−H), 7.56 (t, 1 H, J = 8.4 Hz, Ar−H), 8.08 (d, 1 H, J = 6.7 Hz, Ar−H), 11.93 (s, 1 H, Ar−H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 50.5, 50.5, 53.0, 55.7, 111.7, 112.2, 116.0, 118.3, 121.2, 122.7, 122.9, 123.2, 123.9, 124.6, 131.2, 135.8, 141.6, 144.4 145.3, 152.3; MS *m/z* 467 ($M^+ - 1$). Anal. ($C_{22}H_{22}N_5O_2Br \cdot {}^1/_2H_2O$) C, H, N.

2-[[4-(2-Chlorophenyl)piperazin-1-yl]methyl]-3-bromoimidazo[1,2-*c*]quinazolin-5(6*H*)-one (42b). This was prepared in 44.7% yield by a similar approach which afforded **42a**. The crude product was isolated by column chromatography (solvent system, $CHCl_3$/EtOAc/*n*-hexane = 1:2:2, R_f = 0.21) and recrystallized from MeOH with a small amount of DMF: mp 250 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.67 (s, 4 H, 2 CH_2), 2.92 (s, 4H, 2 CH_2), 7.01 (t, 1 H, J = 9.7 Hz, Ar−H), 7.10 (d, 1 H, J = 8.3 Hz, Ar−H), 7.23−7.39 (m, 4 H, Ar−H), 7.56 (t, 1 H, J = 7.0 Hz, Ar−H), 8.07 (d, 1 H, J = 8.3 Hz, Ar−H), 11.94 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 50.5, 51.2, 52.8, 111.7, 116.0, 121.2, 122.9, 123.2, 123.9, 124.2, 124.5, 128.4, 130.6, 131.4, 135.8, 144.4, 145.3, 149.4; MS *m/z* 473 (M^+). Anal. ($C_{21}H_{19}N_5BrClO$) C, H, N.

2-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-3-bromo-6-methylimidazo[1,2-*c*]quinazolin-5(6*H*)-one (43a). To a mixture of **42a** (0.3 g, 0.64 mmol) in DMF (20 mL) was added sodium hydride (0.05 g, 2.1 mmol). The mixture was stirred at room temperature for 15 min. Methyl iodide (0.056 mL, 0.79 mmol) was added, and the solution was further stirred

at room temperature for 20 min. The solvent was removed in vacuo, and water (20 mL) was added with stirring. The solid that was formed was collected by filtration. The crude product was dried at 60 °C for 12 h and then was recrystallized from EtOH to afford 0.2 g of **43a** in 65% yield: mp 242−243 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87 (s, 4 H, 2 CH_2), 3.81 (s, 4 H, 2 CH_2), 3.74 (s, 3 H, OCH_3), 3.86 (s, 3 H, CH_3), 4.14 (s, 2 H, CH_2), 6.91 (m, 4 H, Ar−H), 7.31 (m, 2 H, Ar−H), 7.58 (t, 1 H, J = 7.2 Hz, Ar−H), 8.36 (d, 1 H, J = 7.8 Hz, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.6, 51.1, 51.6, 53.8, 55.9, 111.7, 113.4, 114.8, 118.8, 121.5, 123.4, 124.3, 124.5, 124.8, 125.4, 131.8, 137.1, 142.0, 144.2, 146.4, 152.9. Anal. ($C_{23}H_{24}N_5BrO_2 \cdot {}^1/_4H_2O$) C, H, N.

2-[[4-(2-Chlorophenyl)piperazin-1-yl]methyl]-3-bromo-6-methylimidazo[1,2-*c*]quinazolin-5(6*H*)-one (43b). This was prepared in 52% yield by a similar approach which afforded **43a**. An analytical sample was recrystallized from methanol and chloroform: mp 237−238 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.85 (s, 4 H, 2 CH_2), 3.07 (s, 4 H, 2 CH_2), 3.75 (s, 3 H, CH_3), 4.13 (s, 2 H, CH_2), 6.94 (t, 1 H, J = 7.6 Hz, Ar−H), 7.00 (d, 1 H, J = 7.6 Hz, Ar−H), 7.19 (t, 1 H, J = 7.5 Hz, Ar−H), 7.34 (m, 3 H, Ar−H), 7.58 (t, 1 H, J = 7.2 Hz, Ar−H), 8.36 (dd, 1 H, J = 1.59, 8.1 Hz, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.6, 51.6, 51.7, 53.8, 113.4, 114.8, 121.0, 124.1, 124.2, 124.5, 124.8, 125.5, 128.1, 129.4, 131.2, 131.8, 137.1, 144.2, 146.4, 150.0; MS m/z 487 (M^+). Anal. ($C_{22}H_{21}N_5BrClO \cdot {}^1/_2H_2O$) C, H, N.

2-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]imidazo-[1,2-*c*]quinazolin-5(6*H*)-one (44a). To a solution of **42a** (0.32 g, 0.68 mmol) in DMF (30 mL) under nitrogen was added 10% Pd/C (0.1 g). A Fisher-Porter bottle was degassed three to four times on the vacuum line and then pressurized to 40 psi with hydrogen. The reaction mixture was shaken at room temperature for 20 h and was then filtered through a bed of Celite. The solvent was removed in vacuo, and acetone (10 mL) was added to the oily residue. The solid was collected by filtration and was recrystallized from CH_3CN and H_2O (20 mL, 1:1) with 3 drops of triethylamine to give 0.17 g of **44a** in 63% yield: mp 212 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.63 (s, 4 H, 2 CH_2), 2.95 (s, 4 H, 2 CH_2), 3.74 (s, 3 H, OCH_3), 4.10 (s, 2 H, CH_2), 6.80−6.94 (m, 4 H, Ar−H), 7.27 (t, 2 H, J = 7.5 Hz, Ar−H), 7.32 (s, 1 H, CH), 7.49 (t, 1 H, J = 7.3 Hz, Ar−H), 8.08 (d, 1 H, J = 7.8 Hz, Ar−H), 11.77 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 50.1, 51.8, 52.5, 55.2, 111.9, 112.5, 115.4, 117.9, 120.8, 122.3, 122.5, 123.2, 127.3, 130.2, 135.1, 141.2, 144.0, 146.3, 152.0. Anal. ($C_{22}H_{23}N_5O_2$) C, H, N.

2-[[4-(2-Chlorophenyl)piperazin-1-yl]methyl]imidazo-[1,2-*c*]quinazolin-5(6*H*)-one (44b). This was prepared in 80% yield by a similar approach which afforded **44a**. An analytical sample was recrystallized from CH_3CN: mp 210 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.67 (s, 4 H, 2 CH_2), 2.98 (s, 4 H, 2 CH_2), 4.13 (s, 2 H, CH_2), 7.02 (t, 1 H, J = 7.7 Hz, Ar−H), 7.15 (d, 1 H, J = 7.0 Hz, Ar−H), 7.30 (m, 4 H, Ar−H), 7.51 (t, 1 H, J = 7.7 Hz, Ar−H), 8.10 (d, 1 H, J = 7.8 Hz, Ar−H), 11.79 (s, 1 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 50.9, 51.7, 52.4, 112.5, 115.5, 120.8, 122.6, 123.3, 123.8, 127.3, 127.6, 128.0, 130.2, 131.6, 135.1, 146.3, 149.0. Anal. HREIMS (exact mass HREMS) calcd for $C_{21}H_{20}N_5OCl$ m/z 393.1352, found 393.1357.

2-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-6-methylimidazo[1,2-*c*]quinazolin-5(6*H*)-one (45a). This was prepared in 61% yield by a similar approach which afforded **43a**. An analytical sample was recrystallized from CH_3CN and water (1:1, 20 mL) with 3 drops of triethylamine: mp 176 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.83 (s, 4 H, 2 CH_2), 3.13 (s, 4 H, 2 CH_2), 3.74 (s, 3 H, OCH_3), 3.86 (s, 3 H, CH_3), 4.20 (s, 2 H, CH_2), 6.84−6.96 (m, 4 H, Ar−H), 7.31 (m, 3 H, Ar−H), 7.55 (t, 1 H, J = 8.1 Hz, Ar−H), 8.36 (dd, 1 H, J = 1.5, 6.3 Hz, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.3, 51.2, 53.5, 53.9, 55.9, 111.7, 111.6, 114.8, 118.8, 121.5, 123.4, 124.4, 124.5, 128.7, 131.1, 132.8, 136.9, 141.9, 144.6, 147.8, 152.8; MS m/z 403 (M^+). Anal. ($C_{23}H_{25}N_5O_2 \cdot {}^1/_4H_2O$) C, H, N.

2-[[4-(2-Chlorophenyl)piperazin-1-yl]methyl]-6-methylimidazo[1,2-*c*]quinazolin-5(6*H*)-one (45b). This was prepared in 56% yield by a similar approach which afforded **43a**: mp 197−199 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.66 (m, 4 H, 2 CH_2), 2.96 (m, 4 H, 2 CH_2), 3.65 (s, 3 H, NCH_3), 4.10 (s, 2 H, CH_2), 7.00−7.62 (m, 8 H, Ar−H), 8.20 (d, 1 H, J = 7.3 Hz, Ar−H). Anal. HREIMS (exact mass HREMS) calcd for $C_{22}H_{22}ON_5Cl$ m/z 407.1513, found 407.1516.

3-Methylimidazo[1,2-*c*]quinazolin-5(6*H*)-one (47). This was prepared in 67% yield by a similar approach which afforded **39**. An analytical sample was recrystallized from ethanol: mp 262−264 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.60 (s, 3 H, CH_3), 7.07 (s, 1 H, Ar−H), 7.22−7.34 (m, 2 H, Ar−H), 7.44−7.57 (m, 1 H, Ar−H), 8.04 (d, 1 H, J = 11 Hz, Ar−H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 11.8, 112.8, 115.4, 122.4, 123.2, 126.5, 129.7, 129.9, 135.1, 143.3, 146.7; MS m/z 199 (M^+). Anal. ($C_{11}H_9N_3O$) C, H, N.

2-Bromo-3-methylimidazo[1,2-*c*]quinazolin-5(6*H*)-one (48). This was prepared in 55% yield by a similar approach which afforded **40**. An analytical sample was recrystallized from CH_3CN: mp 255 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.25 (s, 3 H, CH_3), 7.25−7.31 (m, 2 H, Ar−H), 7.51 (t, 1 H, J = 6.9 Hz, Ar−H), 8.04 (d, 1 H, J = 8.1 Hz, Ar−H), 11.87 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 12.8, 112.0, 115.5, 122.3, 123.3, 130.5, 135.0, 140.3, 144.8. Anal. ($C_{11}H_8N_3BrO$) C, H, N.

2-Bromo-3-(bromomethyl)imidazo[1,2-*c*]quinazolin-5(6*H*)-one (49). This was obtained in 90% yield using a procedure similar to that which afforded **41**. An analytical sample was recrystallized from chloroform: mp 217 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.67 (s, 2 H, CH_2), 7.30 (m, 2 H, Ar−H), 7.55 (t, 1 H, J = 7.7 Hz, Ar−H), 8.07 (d, 1 H, J = 7.1 Hz, Ar−H), 11.98 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 26.1, 98.9, 112.3, 116.0, 123.0, 123.8, 131.5, 131.5, 140.3, 145.2; MS m/z 357 (M^+). Anal. ($C_{11}H_7N_3Br_2O$) C, H, N.

2-Bromo-3-[[4-(2-methoxyphenyl)piperazin-1-yl]methyl]imidazo[1,2-*c*]quinazolin-5(6*H*)-one (50a). This was prepared in 53% yield by a similar approach which afforded **42a**. Compound **50a** (R_f = 0.33, $CHCl_3$/MeOH = 98:2, silica gel) was isolated by column chromatography. An analytical sample was recrystallized from DMF: mp 244−245 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.64 (s, 4 H, CH_2), 2.91 (m, 4 H, CH_2), 3.76 (s, 3 H, OCH_3), 4.01 (s, 2 H, CH_2), 6.89 (m, 4 H, Ar−H), 7.32 (q, 2 H, J = 6.4 Hz, Ar−H), 7.56 (t, 1 H, J = 7.6 Hz, Ar−H), 8.08 (d, 1 H, J = 7.6 Hz, Ar−H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 50.1, 52.5, 55.3, 111.3, 111.8, 115.6, 117.9, 120.8, 122.3, 122.4, 122.7, 123.5, 124.2, 131.0, 135.4, 141.2, 144.0, 144.9, 152.0; MS m/z 467 ($M^+ - 1$). Anal. ($C_{22}H_{22}N_5BrO_2$) C, H, N.

2-Bromo-3-[[4-(2-chlorophenyl)piperazin-1-yl]methyl]-imidazo[1,2-*c*]quinazolin-5(6*H*)-one (50b). This was prepared in 28.7% yield by a similar approach which afforded **42a**. An analytical sample was recrystallized from ethanol: mp 223−224 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.68 (s, 4 H, 2 CH_2), 2.92 (s, 4 H, 2 CH_2), 4.03 (s, 2 H, CH_2), 7.01 (t, 1 H, J = 7.5 Hz, Ar−H), 7.10 (d, 1 H, J = 8.3 Hz, Ar−H), 7.31 (m, 4 H, Ar−H), 7.56 (t, 1 H, J = 7.0 Hz, Ar−H), 8.08 (d, 1 H, J = 6.7 Hz, Ar−H), 11.91 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 50.5, 51.3, 52.8, 111.7, 116.0, 121.2, 122.9, 123.2, 123.9, 124.2, 124.6, 128.0, 128.4, 130.6, 131.4, 135.8, 144.5, 145.3, 149.4; MS m/z 473 (M^+). Anal. ($C_{21}H_{19}N_5BrClO$) C, H, N.

2-Bromo-3-[[4-(2-methoxyphenyl)piperazin-1-yl]methyl]-6-methylimidazo[1,2-*c*]quinazolin-5(6*H*)-one (51a). This was prepared in 57% yield by a similar approach which afforded **43a**. An analytical sample was recrystallized from ethanol and DMF: mp 242−245 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.86 (s, 4 H, 2 CH_2), 3.08 (s, 4 H, 2 CH_2), 3.74 (s, 3 H, OCH_3), 3.86 (s, 3 H, CH_3), 4.13 (s, 2 H, CH_2), 6.91 (m, 4 H, Ar−H), 7.31 (m, 2 H, Ar−H), 7.58 (t, 1 H, J = 8.7 Hz, Ar−H), 8.35 (dd, 1 H, J = 1.4, 7.9 Hz, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.6, 51.1, 51.6, 53.8, 55.9, 111.7, 113.4, 114.8, 118.8, 121.5, 123.4, 124.3, 124.5, 124.6, 124.8, 131.8, 137.1, 141.9, 144.2, 152.9; MS m/z 481 ($M^+ - 1$). Anal. ($C_{23}H_{24}N_5O_2Br$) C, H, N.

2-Bromo-3-[[4-(2-chlorophenyl)piperazin-1-yl]methyl]-6-methylimidazo[1,2-*c*]quinazolin-5(6*H*)-one (51b). This

was prepared in 50% yield by a similar approach which afforded **43a**. An analytical sample was recrystallized from methanol and chloroform: mp 232−233 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.85 (s, 4 H, 2 CH_2), 3.07 (s, 4 H, 2 CH_2), 3.75 (s, 3 H, CH_3), 4.13 (s, 2 H, CH_2), 6.97 (t, 1 H, J = 7.7 Hz, Ar−H), 7.01 (d, 1 H, J = 6.7 Hz, Ar−H), 7.19 (t, 1 H, J = 6.9 Hz, Ar−H), 7.33 (m, 3 H, Ar−H), 7.59 (t, 1 H, J = 7.2 Hz, Ar−H), 8.37 (d, 1 H, J = 7.8 Hz, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.6, 51.6, 51.6, 53.8, 113.4, 114.8, 121.0, 124.1, 124.3, 124.6, 124.8, 125.4, 128.1, 129.4, 131.2, 131.8, 137.1, 144.2, 146.4, 149.9; MS m/z 486.9 (M^+). Anal. ($C_{22}H_{21}N_5BrClO$) C, H, N.

3-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]imidazo-[1,2-*c*]quinazolin-5(6*H*)-one (52a). This was prepared in 81.6% yield by a similar approach which afforded **44a**. An analytical sample was recrystallized from CH_3CN: mp 214−215 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.63 (s, 4 H, 2 CH_2), 2.95 (s, 4 H, 2 CH_2), 3.74 (s, 3 H, OCH_3), 4.10 (s, 2 H, CH_2), 6.82−6.92 (m, 4 H, Ar−H), 7.27 (t, 2 H, J = 7.5 Hz, Ar−H), 7.32 (s, 1 H, ═CH−), 7.49 (t, 1 H, J = 8.5 HZ, Ar−H), 8.08 (d, 1 H, J = 7.7 Hz, Ar−H), 11.75 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 50.1, 51.8, 52.5, 55.2, 111.9, 112.5, 115.4, 117.9, 120.8, 122.3, 122.5, 123.2, 127.3, 130.2, 131.5, 135.1, 141.2, 144.0, 146.3, 152.0. Anal. HREIMS (exact mass HREMS) calcd for $C_{22}H_{23}O_2N_5$ m/z 390.1932, found 390.1933.

3-[[4-(2-Chlorophenyl)piperazin-1-yl]methyl]imidazo-[1,2-*c*]quinazolin-5(6*H*)-one (52b). This was prepared in 70% yield by a similar approach which afforded **44a**. An analytical sample was recrystallized from CH_3CN: mp 221−222 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.65 (s, 4 H, CH_2), 2.97 (s, 4 H, CH_2), 4.10 (m, 2 H, CH_2), 6.74−7.52 (m, 8 H, Ar−H), 8.08 (d, 1 H, J = 7.8 Hz, Ar−H), 11.76 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 50.9, 51.7, 52.4, 112.5, 115.5, 120.8, 122.6, 123.3, 123.8, 127.3, 127.6, 128.0, 130.2, 131.6, 135.1, 144.1, 146.3, 149.0. Anal. HREIMS (exact mass HREMS) calcd for $C_{21}H_{20}N_5ClO$ m/z 393.1352, found 393.1352.

3-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-6-methylimidazo[1,2-*c*]quinazolin-5(6*H*)-one (53a). This was prepared in 72.7% yield by a similar approach which afforded **43a**. An analytical sample was recrystallized from methanol: mp 174−175 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.64 (s, 4 H, 2 CH_2), 2.95 (s, 4 H, 2 CH_2), 3.65 (s, 3 H, CH_3), 3.75 (s, 3 H, OCH_3), 4.08 (s, 2 H, CH_2), 6.89 (m, 4 H, Ar−H), 7.30 (s, 1 H, Ar−H), 7.37 (t, 1 H, J = 7.14 Hz, Ar−H), 7.53 (d, 1 H, J = 7.86 Hz, Ar−H), 7.61 (t, 1 H, J = 7.2 Hz, Ar−H), 8.19 (d, 1 H, J = 6.4 Hz, Ar−H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 31.0, 50.5, 52.5, 53.0, 55.7, 112.2, 113.7, 115.7, 118.3, 121.2, 122.7, 123.2, 123.9, 128.0, 130.9, 132.2, 136.6, 141.6, 143.6, 146.9, 152.4; MS m/z 403 (M^+). Anal. ($C_{23}H_{25}N_5O_2$) C, H, N.

3-[[4-(2-Chlorophenyl)piperazin-1-yl]methyl]-6-methylimidazo[1,2-*c*]quinazolin-5(6*H*)-one (53b). This was prepared in 31% yield by a similar approach which afforded **43a**. An analytical sample was recrystallized from ethanol: mp 200−201 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82 (s, 4 H, 2 CH_2), 3.11 (s, 4 H, 2 CH_2), 3.74 (s, 3 H, CH_3), 4.20 (s, 2 H, CH_2), 6.95 (t, 1 H, J = 6.7 Hz, Ar−H), 7.04 (d, 1 H, J = 8.0 Hz, Ar−H), 7.19 (d, 1 H, J = 7.1 Hz, Ar−H), 7.31 (m, 4 H, Ar−H), 8.36 (d, 1 H, J = 7.9 Hz, Ar−H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 31.3, 51.7, 53.4, 53.8, 114.8, 116.6, 121.0, 124.2, 124.4, 124.5, 128.1, 128.7, 129.3, 129.6, 131.1, 131.2, 132.9, 136.9, 144.6, 149.9; MS m/z 407 (M^+). Anal. ($C_{22}H_{22}N_5ClO$) C, H, N.

3-(Bromomethyl)-2-bromo-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (54). Compound **54** was prepared in 61% yield using a procedure similar to that which afforded **41**. An analytical sample was recrystallized from CH_3CN and $CHCl_3$: mp 221−222 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.16 (s, 2 H, CH_2), 7.68 (t, 1 H, J = 7.32 Hz, Ar−H), 7.93 (m, 1 H, Ar−H), 8.22−8.26 (m, 2 H, Ar−H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 27.0, 106.2, 117.4, 119.4, 127.9, 128.8, 134.1, 134.2, 137.7, 166.3. Anal. HREIMS (exact mass HREMS) calcd for $C_{11}H_6ON_2SCBr_2$ m/e 381.8568, found 381.8570.

3-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-2-bromo-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (55a). Compound **55a** was prepared in 67% yield using a procedure similar to that which afforded **42a**: mp 231 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.82 (s, 4 H, 2 CH_2), 2.99 (s, 4 H, 2 CH_2), 3.79 (s, 3 H, OCH_3), 3.95 (s, 2 H, CH_2), 6.85−6.94 (m, 4 H, Ar−H), 7.64 (m, 1 H, Ar−H), 7.86 (m, 1 H, Ar−H), 8.21 (m, 1 H, Ar−H), 8.75 (d, 1 H, J = 8.67 Hz, Ar−H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 50.5, 52.3, 54.2, 55.7, 101.9, 112.3, 118.4, 119.4, 119.5, 121.2, 123.0, 127.6, 128.1, 133.6, 133.9, 138.6, 141.3, 152.4, 166.7; MS m/z 485 (M^+). Anal. ($C_{22}H_{21}N_4O_2SBr$) C, H, N.

3-[[4-(2-Chlorophenyl)piperazin-1-yl]methyl]-2-bromo-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (55b). Compound **55b** was prepared in 57% yield using a procedure similar to that which afforded **42a**. An analytical sample was recrystallized from ethanol: mp 242−244 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.84 (s, 4 H, 2 CH_2), 3.00 (s, 4 H, 2 CH_2), 3.97 (s, 2 H, CH_2), 7.04 (t, 1 H, J = 6.96 Hz, Ar−H), 7.14 (d, 1 H, J = 6.69 Hz, Ar−H), 7.28 (t, 1 H, J = 7.0 Hz, Ar−H), 7.41 (d, 1 H, J = 7.86 Hz, Ar−H), 7.64 (t, 1 H, J = 7.5 Hz, Ar−H), 7.89 (t, 1 H, J = 7.1 Hz, Ar−H), 8.21 (dd, 1 H, J = 1.53, 6.33 Hz, Ar−H), 8.73 (d, 1 H, J = 8.79 Hz, Ar−H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 51.7, 52.9, 54.8, 103.4, 119.0, 120.2, 121.0, 124.7, 128.1, 128.2, 129.4, 129.7, 131.3, 133.5, 133.7, 139.0, 149.3, 169.1; MS m/z 489 (M^+). Anal. ($C_{21}H_{18}N_4OBrClS$) C, H, N.

3-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (56a). Compound **56a** was prepared in 60% yield using a procedure similar to that which afforded **44a**. An analytical sample was recrystallized from ethanol: mp 243−244 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.73 (s, 4 H, 2 CH_2), 2.97 (d, 4 H, 2 CH_2), 3.78 (s, 3 H, OCH_3), 3.93 (s, 2 H, CH_2), 6.86 (m, 4 H, Ar−H), 7.35 (s, 1 H, ═C−H), 7.62 (t, 1 H, J = 7.5 Hz, Ar−H), 7.86 (t, 1 H, J = 7.02 Hz, Ar−H), 8.21 (d, 1 H, J = 7.86 Hz, Ar−H), 8.58 (d, 1 H, J = 8.49 Hz, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.0, 53.3, 56.0, 58.3, 110.7, 111.8, 118.7, 118.8, 119.8, 121.6, 123.9, 127.9, 129.6, 133.4, 136.0, 138.8, 141.3, 152.8, 168.9; MS m/z 406 (M^+). Anal. ($C_{22}H_{22}N_4O_2S\cdot{}^1/_4H_2O$) C, H, N.

3-[[4-(2-Chlorophenyl)piperazin-1-yl]methyl]-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (56b). Compound **56b** was prepared in 51% yield using a procedure similar to that which afforded **44a**. An analytical sample was recrystallized from ethanol: mp 253−255 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.75 (s, 4 H, 2 CH_2), 2.99 (s, 4 H, 2 CH_2), 3.97 (s, 2 H, CH_2), 7.03 (t, 1 H, J = 8.3 Hz, Ar−H), 7.13 (d, 1 H, J = 6.7 Hz, Ar−H), 7.28 (t, 1 H, J = 8.0 Hz, Ar−H), 7.37 (s, 1 H, ═CH), 7.40 (d, 1 H, J = 8.0 Hz, Ar−H), 7.63 (t, 1 H, J = 7.5 Hz, Ar−H), 7.87 (t, 1 H, J = 8.8 Hz, Ar−H), 8.22 (dd, 1 H, J = 1.7, 7.9 Hz, Ar−H), 8.58 (d, 1 H, J = 8.5 Hz, Ar−H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 51.2, 52.3, 56.7, 111.2, 119.1, 119.3, 121.3, 124.4, 127.4, 128.0, 128.1, 128.5, 130.7, 133.3, 135.7, 138.4, 149.2, 164.8, 168.7; MS m/z 410 (M^+). Anal. ($C_{21}H_{19}N_4OSCl$) C, H, N.

(*S*)-(+)-3-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-5-(methylthio)-2,3-dihydroimidazo[1,2-*c*]quinazoline ((*S*)-(+)-57) and (*R*)-(−)-3-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-5-(methylthio)-2,3-dihydroimidazo[1,2-*c*]quinazoline ((*R*)-(−)-57). These were prepared according to previous published procedures.[19]

(*S*)-(−)-3-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one ((*S*)-(−)-5). A solution of (*S*)-(+)-**57** (1.2 g, 2.85 mmol) and NaOH (5.69 g, 142 mmol) in methanol (60 mL) and water (35 mL) was refluxed for 17 h. Concentrated HCl (6.0 mL, 68 mmol) was added to the cooled solution, and the methanol was evaporated in vacuo. After addition of water (60 mL) the mixture was extracted with dichloromethane (3 × 60 mL). The organic solutions were dried over Na_2SO_4 (5 g), and solvent was evaporated in vacuo. The residue was purified by column chromatography (eluent EtOAc/CH_3OH = 10:1) to give 1.05 g (94.0%) of (*S*)-(−)-**5** as a colorless foam: $[\alpha]^{25}_D$ −33.0 (*c* 1.342, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.65 (br s, 1 H, NH), 7.97 (dd, 1 H, J = 9.2, 1.3 Hz, ArH), 7.47 (t, 1 H, J = 7.5 Hz, ArH), 7.13 (1 H, t, J = 7.2 Hz, ArH), 7.01−6.85 (m, 5 H, ArH), 4.68−4.56 (m, 1 H, (*S*)-CH), 4.25−4.09 (m, 2 H, ═NCH_2), 3.86 (s, 3 H, OCH_3), 3.08−3.03 (m, 5 H), 2.85−2.83 (m, 2 H), 2.73−2.71 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 154.0, 152.8, 150.3, 141.9, 139.6,

133.9, 126.9, 123.7, 123.5, 121.5, 118.8, 115.7, 112.7, 111.7, 60.5, 59.9, 55.9, 55.0, 54.6, 51.2; MS *m/z* 391 (M^+). Anal. ($C_{22}H_{25}N_5O_2 \cdot H_2O$) C, H, N.

(*R*)-(+)-3-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one ((*R*)-(+)-5). This was obtained in 98% yield from (*R*)-(−)-**57** using the similar procedure which yielded in (*S*)-(−)-**5**: $[\alpha]^{25}_D$ +30.9 (*c* 3.178, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.67 (br s, 1 H, NH), 7.89 (d, 1 H, J = 8.8 Hz, ArH), 7.37 (t, 1 H, J = 7.7 Hz, ArH), 7.03 (1 H, t, J = 7.5 Hz, ArH), 6.91−6.75 (m, 5 H, ArH), 4.54−4.49 (m, 1 H, (*S*)-CH), 4.14−4.00 (m, 2 H, =NCH_2), 3.86 (s, 3 H, OCH_3), 3.00−2.94 (m, 5 H), 2.82−2.75 (m, 2 H), 2.73−2.71 (m, 1H), 2.51−2.46 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 153.5, 152.2, 149.7, 141.3, 139.0, 133.3, 126.3, 123.2, 122.9, 121.0, 118.2, 115.1, 112.1, 111.2, 59.9, 59.3, 55.3, 54.4, 54.0, 50.6; MS *m/z* 391 (M^+). Anal. ($C_{22}H_{25}N_5O_2 \cdot 0.75H_2O$) C, H, N.

Methods of Binding Studies. 1. Preparation of Membranes for Binding Studies. Rat brain cortex membranes were prepared for α_1-adrenergic recpetor or α_2-adrenergic receptor binding; rat submaxillary gland members were prepared for α1A binding; rat liver members were prepared for α1B binding; members (BSR-2AH) encoding the human adrenergic α_{2a} receptor were prepared for α_{2a} binding. Tissues were homogenized in 0.32 M sucrose buffered with 50 mM Tris buffer (pH 7.4) in a tissue/buffer ratio of 1:10. After the removal of nuclei by centrifugation at 1000*g* for 10 min, P_2 membranes were pelleted by centrifuging the supernatant at 22000*g* for 20 min. After two rounds of centrifugation at 22000*g* and resuspension in fresh buffer, the membrane suspension (about 2 mg/mL protein) was ready for use.

2. Binding Assays. Adrenergic α_1, α1A, and α1B receptor competition binding assays (in triplicate) were carried out with 0.2−0.25 nM [^{3}H]prazosin and in a final volume of 1.0 mL of Tris buffer at pH 7.4 for 30 min at room temperature, using 10 μM phentolamine to determine nonspecific binding. The concentrations of each compound for competition binding were in the range of 0.1−200 nM. α_2-Adrenergic receptor competition binding assays (in triplicate) were carried out with 1 nM [^{3}H]clonidine in the presence of 10 mM $MgCl_2$ in a final volume of 1.0 mL of Tris buffer at pH 7.4 for 30 min at room temperature, using 10 μM clonidine to determine nonspecific binding. The concentrations of each compound for competition binding were in the range of 1−100 μM. After binding had reached equilibrium, incubations were terminated by collecting the membranes on Whatman GF/B filters; the filters were washed twice with 5 mL of 50 mM Tris buffer (pH 7.4) at 4 °C. The amount of membrane protein used in each assay was in the range of 300−400 μg, as determined by the method of Lowry.[24]

The competition binding assays were analyzed with the McPherson program,[25] which is a modification of the LIGAND progam originally written by Munson and Rodbard.[26] K_i value (the equilibrium dissociation constant of tested compound) was obtained by this analysis.

3. Antihypertensive Activity. Male 16-week old spontaneously hypertensive rats (SHR) weighing 250−300 g were anesthetized with urethane (0.6 g/kg, ip) and chloral hydrate (0.4 g/kg, ip). The left femoral artery and vein were cannulated for the measurement of blood pressure (BP) and intravenous administration of drugs, respectively. The catheter for BP measurement was connected to a pressure transducer (Statham P23 ID, Gould), and the arterial BP was continuously recorded on a biotechometer (RS 3400, Gould). The heart rate (HR) was triggered from the arterial pressure through a tachometer (Grass model).

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