Studies on Quinazolines. 5.[1] 2,3-Dihydroimidazo[1,2-c]quinazoline Derivatives: A Novel Class of Potent and Selective α_1-Adrenoceptor Antagonists and Antihypertensive Agents†

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A series of 2-[(substituted phenylpiperazin-1-yl)methyl]- and 2-[(substituted phenylpiperidin-1-yl)methyl]-2,3-dihydroimidazo[1,2-c]quinazolin-5(6*H*)-ones or -5(6*H*)-thiones, and 3-[(substituted phenylpiperazin-1-yl)methyl]-2,3-dihydroimidazo[1,2-c]quinazoline derivatives were synthesized, as conformationally restricted analogues of SGB-1534 and ketanserin, for evaluation as α-antagonists and antihypertensive agents. Most compounds containing a (substituted phenylpiperazinyl)methyl side chain displayed high binding affinity for α_1-adrenoceptor with no significant activity at α_2-sites. Compounds having a (substituted phenylpiperazinyl)methyl at the 3-position of 2,3-dihydroimidazo[1,2-c]quinazolin-5(6*H*)-one ring system had a better activity than those with the same substituent at the 2-position. Structure–activity relationships for α_1-adrenoceptor affinity are presented and indicate that compounds with substitution at the ortho position on the benzene ring of the phenylpiperazine side chain moiety are more potent than those without substitution and/or substitutions at the 3- and 4-positions. Computer-assisted superimposition of SGB-1534 and **20b** showed little structural correspondence between the quinazolinone and 2,3-dihydroimidazo[1,2-c]quinazoline nucleus, and specific interactions of these molecular fragments with the receptor protein appear unlikely. Antihypertensive activity was evaluated *via* intravenous administration of each compound to spontaneously hypertensive rats, and compounds (**16a**, **16b**, **20b**, and **28b**) illustrated similar efficacy to SGB-1534 when assessed after 6 h. The pA_2 value for **16a** against phenylephedrine in rat aorta was much higher than that of prazosin. On the basis of α_1-adrenoceptor affinity/selectivity in vitro and duration of antihypertensive action in vivo, compounds **20b** and **28b** warrant further evaluation.

Introduction

Hypertension is a serious risk factor for cerebrovascular disease and heart disease in developed countries. Although there are several antihypertensive drugs clinically available, due to the different origin and pathology of hypertension, it is difficult to control all types of hypertension through the use of only one drug, and each antihypertensive agent has its own side effects. Thus, the development of new and effective antihypertensive drugs with different modes of action is still required.

A literature survey reveals that a variety of antihypertensive agents contain quinazoline and quinazolinone ring systems. For example, prazosin (1), a 2-substituted quinazoline derivative, has been proven effective in the clinic, acting as a α_1-adrenoceptor antagonist.[2] Other 3-substituted quinazolinones, such as SGB-1534 (**2**)[3] and ketanserin (**3**),[4] have been found to have antihypertensive activities mediated via α-adrenoceptor and serotonic receptor anatgonism, respectively. Interestingly, ketanserin and SGB-1534 have the same structural skeleton, and the only difference between these two compounds is the substituent at the 3-position where ketanserin has a benzoylpiperidine side chain and SGB-1534 contains a (methoxyphenyl)piperazine ring. On the other hand, a variety of structural analogs to SGB-1534 or ketanserin, made simply by replacing the quinazolinon-2,4-dione with different heterocycles,[5-7] such as thienopyrimidinediones (**4**)[8] and pyrimido[5,4-*b*]indole (**5**)[9] derivatives, have been proven effective in lowering blood pressure via antagonizing the α_1-adrenoceptor as well. Thus, the 1-arylpiperazine side chain is considered to be an essential moiety for the lowering of blood pressure.[10]

Recently, it was reported that the antihypertensive effects of the quinazoline derivatives were associated with favorable changes in serum cholesterol profile,[11] and several α_1-antagonists are currently being studied for the treatment of dysuria[12] secondary to benign prostatic hypertrophy. During a course of our synthetic studies on the antihypertensive effects of the fused quinazolinone ring system and on the basis of compounds **2–5** as precendent, we reasoned that the tricyclic condensed quinazoline derivatives of the general structures shown in Chart I, which would possess a restricted structural feature necessary to elicit the biological activities of both ketanserin and SGB-1534, would be potentially active molecules. A perusal of literature indicates that the angular tricyclic condensed quinazolinone heterocycles, such as 2,3-dihydroimidazo[1,2-c]quinazolin-5(6*H*)-one derivatives with the appropriate arylpiperazine side chain locating at the 2- or 3-position, received little attention. We reasoned that the hydrophobic character of the 2,3-dihydroimidazo[1,2-c]quinazolin-5(6*H*)-one moiety may provide for better binding to the receptor site. In fact, it has been shown that there is a hydrophobic domain adjacent to the α_1-adrenoceptor,[13] and exploitation of such hydrophobic character of the α_1-adrenoceptor has resulted in the discovery of pyrimido[5,4-*b*]indole derivatives (**5**)[9] as potent α_1-adrenoceptor antagonists. This paper will de-

† This manuscript is dedicated to Professor Leroy B. Townsend on the occasion of his 60th birthday.

‡ Department of Pharmacology.

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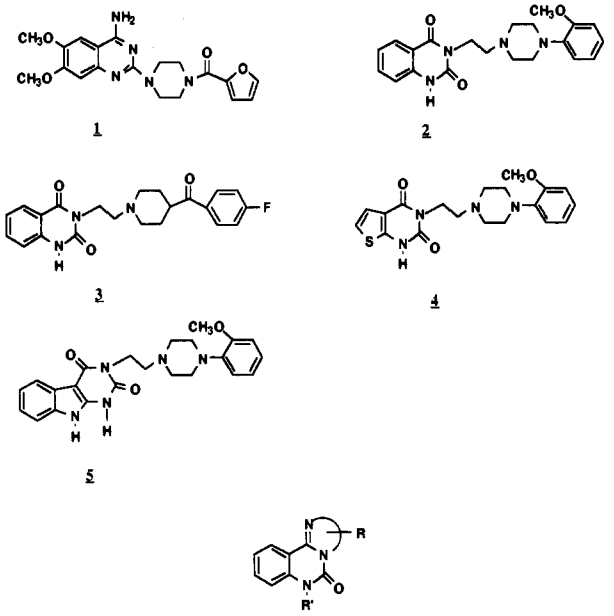
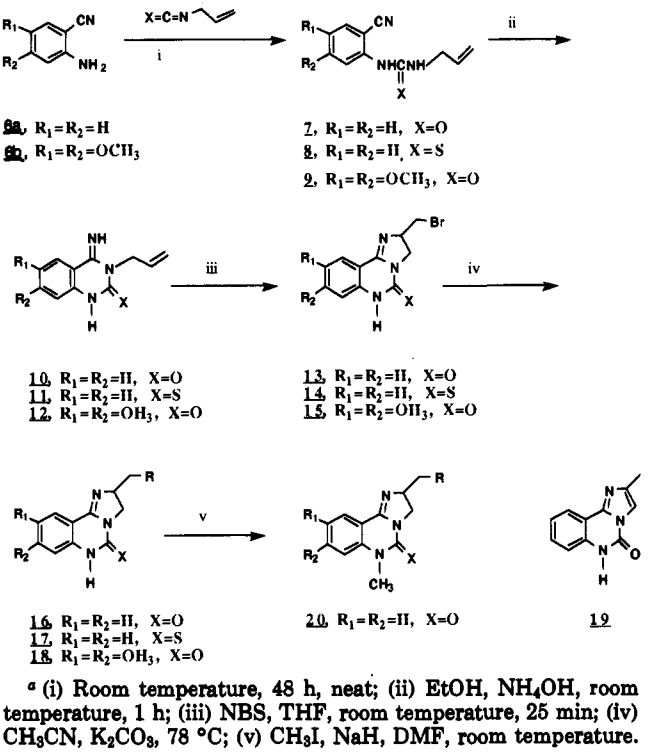
Chart I. Target Compounds



Scheme I[a]



[a] (i) Room temperature, 48 h, neat; (ii) EtOH, NH_4OH, room temperature, 1 h; (iii) NBS, THF, room temperature, 25 min; (iv) CH_3CN, K_2CO_3, 78 °C; (v) CH_3I, NaH, DMF, room temperature.

scribe our efforts toward the synthesis of these conformationally restricted analogues of SGB-1534 as potent and selective α_1-adrenoceptor antagonists.

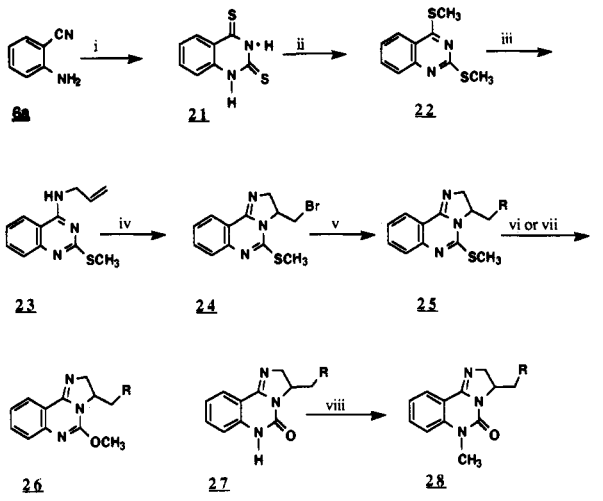
Chemistry

At the outset, we initiated the synthesis of compounds **16–20** outlined in Scheme I. Treatment of anthranilonitrile (**6a**) with allyl isocyanate neat at room temperature afforded a quantative amount of 2-(3-allylureido)benzonitrile (**7**). The ring closure of the resulting urea **7** was effected by using ammonia hydroxide furnishing 3-allyl-4-iminoquinazolin-2(1*H*)-one (**10**). Subsequently, compound **10** was subjected to bromocyclization with NBS in THF at room temperature, and the solid was collected by filtration. The infrared spectrum of the product illustrated a strong absorption peak at 1687 (C=O) cm^{-1}, indicating a carbonyl group exisiting in the molecule. Thus the structure of the product was assigned to be the angular 2-(bromomethyl)-2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one (**13**). Treatment of **13** with 2 equiv of various amines in acetonitrile afforded **16a–o** in a good yield (Scheme I). It shall be noted that a reaction of **13** with 1-piperonylpiperazine afforded not only **16h** (67% yield) but also 2-methyl-2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one (**19**) (23% yield). 2-[(4-Phenylpiperazin-1-yl)methyl]-8,9-dimethoxy-2,3-dihydroimidazo[1,2-*c*]-quinazolin-5(6*H*)-one (**18**) was also prepared starting from 3,4-dimethoxybenzonitrile (**6b**) by the same approach.

Similarly, 3-allyl-4-iminoquinazoline-2(1*H*)-thione (**11**) was prepared in 44% yield by a direct condensation of **5** with allyl isothiocyanate without isolation of the resulting thioureido **8**. A treatment of **11** with *N*-bromosuccinimide afforded a hydrochloride salt of 2-(bromomethyl)-2,3-dihydroimidazo[1,2-*c*]quinazoline-5(6*H*)-thione (**14**) in 40% yield. Although the early literature described that iodocyclization of *N*-allylthioureas led efficiently to the formation of dihydrothiazoles,[14] the formation of **14** was achieved through the 4-imino nitrogen addition to the allyl group instead of the participation of the neighboring 2-sulfur atom. The structural determination of **14** was based on ^{13}C NMR spectrum which revealed an aborption at δ 206.07, indicative of the existence of a thiocarbonyl group in the molecule. A substitution reaction of compound **14** with 1-phenylpiperazine under above the conditions furnished 2-[(4-phenylpiperazin-1-yl)methyl]-2,3-dihydroimidazo[1,2-*c*]quinazoline-5(6*H*)-thione (**17**) in 76% yield. Methylation of **16a–d** with methyl iodide was performed in the presence of a base under an ice-cooling bath, affording compounds **20a–d** in good yield. However, if the same reaction was conducted at room temperature, it gave a complex mixture. Analysis of the ^1H NMR spectra of **16a–d** illustrated a sharp singlet band absorption at around δ 3.36–3.47 which is due to NCH_3 protons and suggests that *N*-methylation occurred.

To elaborate and study the hypotensive effect of the side chain at the 3-position of 2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one, *N*-allylamidine, such as 4-(allylamino)-2-(methylthio)quinazoline (**23**), was subjected to perform a bromocyclization with NBS as well. Compound **23** was prepared in a good yield by an initial treatment of **5** with carbon disulfide in pyridine, affording quinazoline-2,4(1*H*,3*H*)-dithione (**21**), which was then methylated with methyl iodide and subsequently reacted with the resulting dimethylthioquinazoline (**22**) with allylamine in a stainless bomb at 130 °C. Compound **23** then underwent bromocyclization with NBS under similar conditions affording 3-(bromomethyl)-5-(methylthio)-2,3-dihydroimidazo[1,2-*c*]quinazoline (**24**) in a quantitative yield. 3-[(4-Substituted phenylpiperazin-1-yl)methyl]-5-(methylthio)-2,3-dihydroimidazo[1,2-*c*]quinazolines (**25a–e**) were obtained in a reasonable yield by reacting **24** with 4-phenyl-1-piperazine or 4-(substituted phenyl)-1-piperazines (Scheme II). When compounds **25a–e** were heated to reflux in methanol in the presence of sodium hydroxide, 3-[(4-substituted phenylpiperazin-1-yl)methyl]-2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-ones (**27a–e**) were obtained in good yield. However, repeating the same reaction by heating the reaction mixture at 50 °C instead of refluxing temperature, 3-[(4-substituted phenylpiperazin-1-yl)methyl]-5-methoxy-2,3-dihydroimidazo[1,2-*c*]quinazo-

Scheme II[a]



[a] (i) CS_2, pyridine, 70 °C, 6 h, 92%; (ii) MeI, aqueous NaOH, room temperature, 12 h, 93%; (iii) allylamine, CH_3CN, 130 °C, 36 h, 84%; (iv) NBS, CH_3CN, room temperature, 12 h, 85%; (v) amines (2 equiv), CH_3CN, 100 °C, 24 h; (vi) MeOH, NaOH, 50 °C, 6 h (give **26**); (vii) MeOH, NaOH, 70 °C, 6 h (give **27**); (viii) NaH, MeI, CH_3CN, 0 °C.

lines (**26a–e**) were isolated in good yield. *N*-Methylation of compounds **27a–d** with methyl iodide in the presence of sodium hydride at room temperature furnished 3-[(4-substituted phenylpiperazin-1-yl)methyl]-6-methyl-2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-ones (**28a–d**) in good yield.

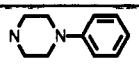
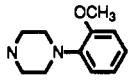
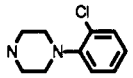
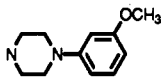
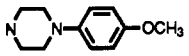
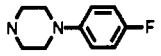
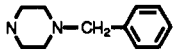
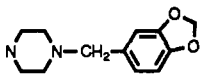
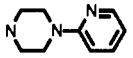
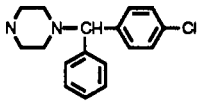
Results and Discussion

Structure–Activity Relationships for α-Adrenoceptor Affinity in Vitro. In Tables VI and VII, the effects of variation of the phenylpiperazine and/or phenylpiperidine moiety at the 2- or 3-position of the 2,3-dihydroimidazo[1,2-*c*]quinazoline ring system on α_1-adrenoceptor binding affinity are presented. These were determined in competition binding experiments. In the present study, we found some selective compounds with high affinity for α_1-adrenoceptor. The most important structural feature in these molecules which seemed to be necessary for receptor binding is the presence of an ortho substituent on the phenyl ring at the N-4 position of the piperazine moiety of the side chain being attached to either the 2- or the 3-position of 2,3-dihydroimidazo[1,2-*c*]quinazoline ring system.

Comparision of entries **16a–o** in the series of 2-substituted methyl-2,3-dihydroimidazo[1,2-*c*]quinazoline derivatives (Table VI) indicated that while the unsubstituted compound **16a** showed a K_i value of 2.01 nM for the α_1-adrenoceptor, the presence of a substituent (methoxy) in the meta or para position of the phenyl ring (**16d** and **16e**) dramatically reduced the affinity. Substitution of an *o*-methoxy group (**16b**) increased the affinity about 5-fold (K_i = 1.3 nM), and a similar enhancement in affinity was seen in **16c** when the ortho position was substituted with a chlorine atom. This is in agreement with previous studies that the introduction of methoxy or chloro substituents at ortho position on the phenyl ring of the phenylpiperazine side chain on different heterocycles gives the highest affinity for α_1-adrenoceptor[8,9] or other receptors.[16] These changes in affinity could be partially due to the steric effects. Probably meta or para substituents create steric bulk in a forbidden volume of the receptor site, while ortho substituents arrange the phenyl ring and the piperazine group into a conformation which better fits the binding site. However, the presence of a fluorine atom at the para position (**16f**) is 10-fold less potent than the unsubstituted compound **16a**. Thus the steric effect might lend some support to the fact that the affinity of **16e** was dramatically reduced and that of **16f** was just slightly reduced. Electronic effects may also be involved. Meanwhile, replacing the piperazine moiety with piperidine, such as compounds **16k–o**, did not show better affinity than those of compounds with a piperazine side chain. Activity was also dramatically reduced in compounds **16g**, **16h**, and **16j**, while replacing the phenyl ring with a benzyl group or benzyl derivatives reduced potency about 100–1000-fold compared to compound **16a**. Incorporation of a nitrogen (**16i**) in the phenyl ring of the side-chain moiety reduced potency 48-fold compared to the parent compound **16a**. When the 5-carbonyl group of **16a** was replaced with thiocarbonyl moiety, the affinity of compound **17** (K_i = 158 nM) for α_1-adrenoceptors is 79-fold less than that of **16a**. Interestingly, introduction of two methoxy groups (**18**) into the benzene ring of the 2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one ring system was detrimental, producing a 15-fold decrease in potency. However, these two methoxy groups are believed to play an important role in lowering blood pressure in the case of the prazosin series.[17] The substitution of a methyl group for the hydrogen atom of the NH function on the 2-substituted methyl-2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one system had a significant effect on the affinity (Table VII); the methylated compound **20b** with K_i = 0.37 nM was 3-fold better that that of **16b**, and compound **20c** with K_i = 0.68 nM was slightly better than that of **16c**, indicating that the NH may not function as a hydrogen-bond donor in the α_1 protein–ligand complex. Unexpectedly, the methylated compound **20a** is slightly less potent than the corresponding **16a**.

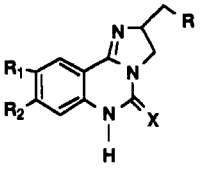
To further explore the effects of the phenylpiperazine methyl substituent at 3-position of the molecular skeleton on affinity, compounds **27a–e** were prepared. The effects of the phenylpiperazine side chain at the 3-position of 2,3-dihydroimidazo[1,2-*c*]quinazoline derivatives on α_1- and α_2-adrenoceptor binding affinity are presented in Table VII. Comparison of compounds **27a–c** with compounds **16a–c** illustrated that the effect of phenylpiperazine side chain at the 3-position series had better affinity than those of the side chain at the 2-position series, respectively. Compounds **25–26** were the key intermediates toward the preparation of **27a–e**, and they were subjected to competition binding assay as well. Surprisingly, these compounds display high affinity and selectivity for α_1-adrenoceptors, and compounds **26b** (K_i = 0.07 nm) and **26c** (K_i = 0.11 nM) are the most potent compounds in this series and show better affinity than those of prazosin (**1**) and SGB-1534 (**2**). Similarly, the isomeric 3- and 4-methoxyphenyl compounds (**25d–e**, **26d–e**, and **27d–e**) were much less potent than their 2-methoxy counterparts (**25b**, **26b**, and **27b**); the 4-methoxy compounds (**25e**, **26e**, and **27e**) were the least potent. The methylated products **28b** (K_i = 0.36 nM) and **28c** (K_i = 0.068 nM) were equal to or more potent than those of the corresponding compounds **27b** and **27c**. However, while computer-assisted superimposition of **20b** with SGB-1534 demonstrates the obvious equivalence of the phenylpiperazine side-chain moiety, there appears to be little structural

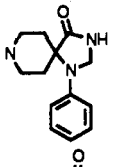
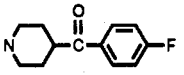
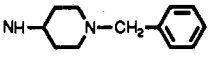
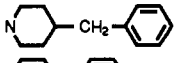
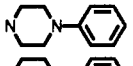
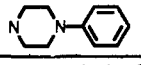
Table I. Physical Data for 2-[(Substituted piperazin-1-yl)methyl]imidazo[1,2-*c*]quinazolin-5(6*H*)-ones

no.	R	solvents[a]	yield,[b] %	mp, °C	formula[c]
16a		CH_3CN/MeOH	76	257–258	$C_{21}H_{23}N_5O$
16b		CH_3CN/MeOH	66	226–227	$C_{22}H_{25}N_5O_2$
16c		CH_3CN/MeOH	67	235–236	$C_{21}H_{22}N_5OCl$
16d		CH_3CN/MeOH	88	>300	$C_{22}H_{25}N_5O_2$
16e		CH_3CN	54	229–231	$C_{22}H_{25}N_5O_2$
16f		CH_3CN/MeOH	61	248–249	$C_{21}H_{22}N_5OF$
16g		CH_3CN/MeOH	64	222–224	$C_{22}H_{25}N_5O$
16h		CH_3CN/MeOH	67	236–238	$C_{23}H_{23}N_5O_3 \cdot HBr \cdot H_2O$
16i		CH_3CN/MeOH	81	242–243	$C_{20}H_{22}N_6O$
16j		CH_3CN	40	245–246	$C_{23}H_{26}N_5OCl$

[a] The solvents which compounds are recrystallized from. [b] Yields are not optimized and represent the conversion of 13 to 16. [c] The analyses are within ±0.4% of the theoretical values.

Table II. Physical Data for 2-Substituted Methylimidazo[1,2-*c*]quinazolin-5(6*H*)-ones

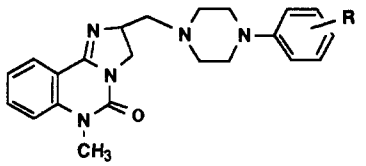


no.	R	X	R_1	R_2	yields,[a] %	mp, °C (solvent)[b]	formula[c]
16k		O	H	H	74	250–251 (CH_3CN)	$C_{24}H_{26}N_6O_2 \cdot {}^1/_4H_2O$
16l		O	H	H	81	220–221 (acetone)	$C_{23}H_{23}N_4O_2F$
16m		O	H	H	73	203–205 (CH_3CN/MeOH)	$C_{21}H_{28}N_4O$
16n		O	H	H	76	206–208 (CH_3CN/MeOH)	$C_{23}H_{27}N_5O$
16o		O	H	H	62	225–227 (CH_3CN/MeOH)	$C_{23}H_{28}N_4O$
17		S	H	H	48	162–163 (CH_3CN)	$C_{21}H_{23}N_5S$
18		O	OCH_3	OCH_3	90	283–284 (ethanol)	$C_{23}H_{27}N_5O_3$

[a] Yields are not optimized and represent the conversion of 13 to 16, 14 to 17, or 15 to 18. [b] The solvents which compounds are recrystallized from. [c] The analyses are within ±0.4% of the theoretical values.

correspondence between the quinazolinone and 2,3-dihydroimidazo[1,2-*c*]quinazoline nucleus[18] (Figure 1). It has been proposed by De Marinis[19] that the principal requirements for ligand binding to the α_1-adrenoceptor is

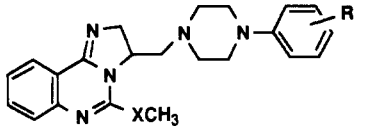
Table III. Physical Data for 2-[(Substituted phenylpiperazinyl)methyl]-3-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one Derivatives



no.	R	yield,[a] %	mp, °C	solvent[b]	formula[c]
20a	H	76	185–186	CH_3CN	$C_{22}H_{25}N_5O$
20b	2-OCH_3	85	157–158	CH_3CN	$C_{23}H_{27}N_5O_2$
20c	2-Cl	63	165–166	CH_3CN	$C_{22}H_{24}N_5ClO$

[a] Yields are not optimized and represent the conversion of 16a–c to 20a–c. [b] The solvents which compounds are recrystallized from. [c] The analyses are within ±0.4% of the theoretical values.

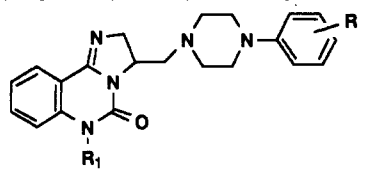
Table IV. Physical Data for 3-[(Substituted phenylpiperazinyl)methyl]-2,3-dihydroimidazo[1,2-c]quinazoline Derivatives



no.	X	R	yield,[a] %	mp, °C	solvent[b]	formula[c]
25a	S	H	56	133–134	CH_3CN	$C_{22}H_{25}N_5S$
25b	S	2-OCH_3	82	174–175	CH_3CN	$C_{23}H_{27}N_5SO$
25c	S	2-Cl	45	184–185	EtOH	$C_{22}H_{24}N_5ClS$
25d	S	3-OCH_3	57	138–139	CH_3CN	$C_{23}H_{27}N_5SO$
25e	S	4-OCH_3	54	133–135	CH_3CN	$C_{23}H_{27}N_5SO$
26a	O	H	75	146–147	CH_3CN	$C_{22}H_{25}N_5O$
26b	O	2-OCH_3	60	171–172	CH_3CN	$C_{23}H_{27}N_5O_2$
26c	O	2-Cl	84	148–149	CH_3CN	$C_{22}H_{24}N_5ClO$
26d	O	3-OCH_3	90	99–100	CH_3CN	$C_{23}H_{27}N_5O_2$
26e	O	4-OCH_3	90	149–150	CH_3CN	$C_{23}H_{27}N_5O_2$

[a] Yields are not optimized and represent the conversion of 24a–e to 25a–e and 25a–e to 26a–e, respectively. [b] The solvents which compounds are recrystallized from. [c] The analyses are within ±0.4% of the theoretical values.

Table V. Physical Data for 3-[(Substituted phenylpiperazinyl)methyl]-2,3-dihydro[1,2-c]quinazolin-5(6H)-one Derivatives



no.	R_1	R	yield,[a] %	mp, °C	solvent[b]	formula[c]
27a	H	H	93	252–253	EtOH	$C_{21}H_{23}N_5O$
27b	H	2-OCH_3	34	211–212	EtOH	$C_{22}H_{25}N_5O_2$
27c	H	2-Cl	68	227–228	EtOH	$C_{21}H_{22}N_5ClO$
27d	H	3-OCH_3	90	200–201	EtOH	$C_{22}H_{25}N_5O_2$
27e	H	4-OCH_3	99	250–251	DMF	$C_{22}H_{25}N_5O_2$
28a	CH_3	H	92	173–174	CH_3CN	$C_{22}H_{25}N_5O$
28b	CH_3	2-OCH_3	65	147–148	CH_3CN	$C_{23}H_{27}N_5O_2$
28c	CH_3	2-Cl	90	154–155	EtOH	$C_{22}H_{24}N_5ClO$
28d	CH_3	3-OCH_3	84	139–140	CH_3CN	$C_{23}H_{27}N_5O_2$

[a] Yields are not optimized and represent the conversion of 25a–e to 27a–e and 27a–d to 28a–d, respectively. [b] The solvents which compounds are recrystallized from. [c] The analyses are within ±0.4% of the theoretical values.

the presence of an electron-rich aromatic area coupled to a protonable nitrogen atom at a suitable distance. On this basis, we thus reasoned that while these molecular features are particularly well accepted by the α_1-adrenoceptor, specific interaction between the protonable phenylpiperazine side chain and receptor protein may be essential and induce the α-adrenoceptor protein conformational change to fit the electron-rich aromatic moiety. This lends some support to the previous assumption that 1-arylpiperazine side chain is considered to be an essential moiety for the lowering of blood pressure.[10]

Some of the compounds in Tables VI and VII also displayed affinity for α_2-adrenoceptor binding sites, but most compounds had lower affinity than for α_1-adrenoceptors. Some compounds, such as **20b** and **28b**, still displayed high α_1/α_2-selectivity ratios, similar to SGB-1534, and such weak α_2-receptor affinity would be of little pharmacological significance (vide infra). It shall be noted that α_1/α_2-selectivity ratios of (*o*-methoxyphenyl)piperazine (**20b**, **25b**, and **26b**) are higher than that of *o*-chloro derivatives (**20c**, **25c**, and **26c**).

Functional α_1-antagonist activity against phenylephedrine was determined for compound **16a** in the rat aorta. Compound **16a** and SGB-1534 are essentially equipotent, competitive antagonists (pA_2: **16a**, 9.82 ± 0.19, slope = 1.11 ± 0.09; SGB-1534, 9.63 ± 0.05, slope = 1.53 ± 0.06) of the α_1-mediated vasoconstrictor effects of phenylephedrine.[20] However, the pA_2 value for **16a** against phenylephedrine in the rat aorta was much higher than that of prazosin (pA_2: 8.34 ± 0.10, slope = 1.04 ± 0.04). In order

Table VI. SHR Results and Affinity of Compounds 16–18 for Adrenoceptors

		SHR results:[a] MBP, mmHg		K_i, nM[b]		
no.	dose[c]	1 h	6 h	α_1-AR	α_2-Ar	α_2/α_1
16a	1.0	−57.5 ± 2.5	−44.5 ± 0.5			
	0.5	−49.3 ± 1.5	−32.5 ± 2.5	2.01 ± 0.09	3860 ± 640	1920
	0.25	−23.1 ± 2.7	−8.75 ± 5.7			
16b	0.5	−20 ± 2.5	−18.8 ± 1.3	1.3 ± 0.5	3450 ± 329	2654
16c	1.0	−40.7 ± 9.7	−12.6 ± 3.4			
	0.5	−25.5 ± 3.4	−5.7 ± 1.5	1.1 ± 0.05	3166 ± 396	3015
16d	4.0	−20.3 ± 8.2	−8.5 ± 2.6	ND[e]	ND	ND
16e	4.0	–[d]	–	>100	ND	ND
16f	4.0	–		14.4	391	27
16g	4.0	−43.7 ± 5.2	–	850	>10,000	>11
16h	4.0	–	–	>100	ND	ND
16i	4.0	–	–	95.9 ± 5.2	ND	ND
16j	4.0	–	–	ND	ND	ND
16k	4.0	–	–	ND	ND	ND
16l	4.0	−30 ± 7.3	−13.8 ± 8.9	ND	ND	ND
16m	4.0	–	–	251.2 ± 28.1	ND	ND
16n	4.0	–	–	586 ± 9	ND	ND
16o	4.0	−30.6 ± 4.7	–	35.8 ± 8.6	5011 ± 11	140
17	4.0	−33.9 ± 9.7	−22.5 ± 7.6	158 ± 15	ND	ND
18	4.0	−38.2 ± 5.7	−12.6 ± 5.0	30 ± 10	1694	54
SGB-1534	0.5	−33.9 ± 3.3	−31.7 ± 3.5	0.25 ± 0.06	1599 ± 324	6396
prazosin				0.19 + 0.02[f]	4830 + 1280	25421

[a] Spontaneously hypertensive rat (SHR) results from groups of four to six animals. [b] The K_i values are mean (±SEM) of three to five separate experiments. [c] Compound was given to SHR by intravenous administration. [d] Symbol "–" means that the lowering mean blood pressure did not last more than $^1/_2$ h by intravenous administration of compounds to SHR. [e] ND, not detected. [f] Reference 17.

Table VII. SHR Results and Affinity of Compounds 20–28 for Adrenoceptors

		SHR results[a]:MBP, mmHg		K_i, nM[b]		
no.	dose[c]	1 h	6 h	α_1-AR	α_2-AR	α_2/α_1
20a	0.5	–[d]	–	10.5 ± 0.21	3334 ± 10	1270
20b	0.5	−38.4 ± 3.4	−28.4 ± 3.4	0.37 ± 0.12	1740 ± 173	4902
20c	0.5	−27.5 ± 6	−22.5 ± 5	0.68 ± 0.26	473 ± 33	696
25a	1.0	–	–	>10	ND[e]	
15b	1.0	–	–	0.34 ± 0.09	1778 ± 286	5229
25c	1.0	–	–	0.34 ± 0.06	223 ± 55	656
25d	1.0	–	–	48.8 ± 2.4	8356 ± 588	171
25e	1.0	–	–	>100	ND	
26a	1.0	–	–	1.35 ± 0.44	952 ± 195	705
26b	0.5	−17.2 ± 8.9	–	0.07 + 0.007	472 + 34	6734
26c	0.5	−28.3 ± 6.7	–	0.11 ± 0.02	116 ± 15	1055
26d	4.0	–	–	>100	ND	
26e	4.0	–	–	>100	ND	
27a		ND		1.7 ± 0.5	962 ± 29	566
27b	0.5	–	–	0.21± 0.02	593 ±6	2824
27c	0.5	−14.6 ± 3.7	−15 ± 1.1	0.58 ± 0.07	387 ± 63	667
27d	4.0	–	–	5.76 + 0.48	302 + 37	52
27e	4.0	–	–	>50	ND	
28a	1.0	−23.3 ± 1.7	−20 ± 2.5	15 ± 1.5	ND	
28b	0.5	−32.5 ± 10	−28.3 ± 9	0.36 ± 0.05	1419 ± 74	3942
28c	0.5	−8.3 ± 2.8	−5.9 ± 0.9	0.068 ± 0.006	810 ± 50	11912
	2.0	−24 ± 3.1	−14 ± 2.3			
28d	4.0	–	–	19.4	ND	

[a] Spontaneously hypertensive rat (SHR) results from groups of four to six animals. [b] The K_i values are means (±SEM) of three to five separate experiments. [c] Compound was given to SHR by intravenous administration. [d] Symbol "–" means that the lowering mean blood pressure did not last more than $^1/_2$ h by intravenous administration of compounds to SHR. [e] ND, not detected.

to determine the antihypertensive effect mediated through blocking α_1-adrenoceptor and/or 5-HT_2 receptor, effects of **16a** on pressor response to phenylephedrine and 5-HT were performed in conscious SHR. The IC_{50} of ketanserin and **16a** on the contractile arteries were 5.73 nM vs 0.44 μM and 27.8 nM vs 0.36 nM, respectively.[20] The blocking effect of **16a** on pressor responses to phenylephedrine was more pronounced than that to 5-HT.

Structure–Activity Relationships for Antihypertensive Activity. The compounds listed in Tables VI and VII were evaluated for blood pressure lowering activity in the anesthetized spontaneously hypertensive rat (SHR) by an intravenous administration of various doses of each compound for initial screening, and the results are reported in the tables as maximum change of the mean blood pressure (MBP) at a single dose that was measured over either a 1- or a 6-h period. Several members of the series, **16a–c**, **20b–c**, **27c**, and **28b–c**, proved to be potent, long-acting antihypertensive agents in the rat with activity at the 6-h time point. The antihypertensive potencies of these compounds did not totally agreed with functional α_1-antagonist data; the compounds with less affinity were poorly effective; compounds with a methoxy group (**16b**, **20b**, **26b**, and **28b**) or with a chloro atom (**16c**, **20c**, **26c**, **27c**, and **28c**) or at the ortho position of the 4-phenylpiperazine side chain demonstrated significant antihypertensive activity. This is also in agreement with previous studies that the (*o*-substituted phenyl)piperazine-con-

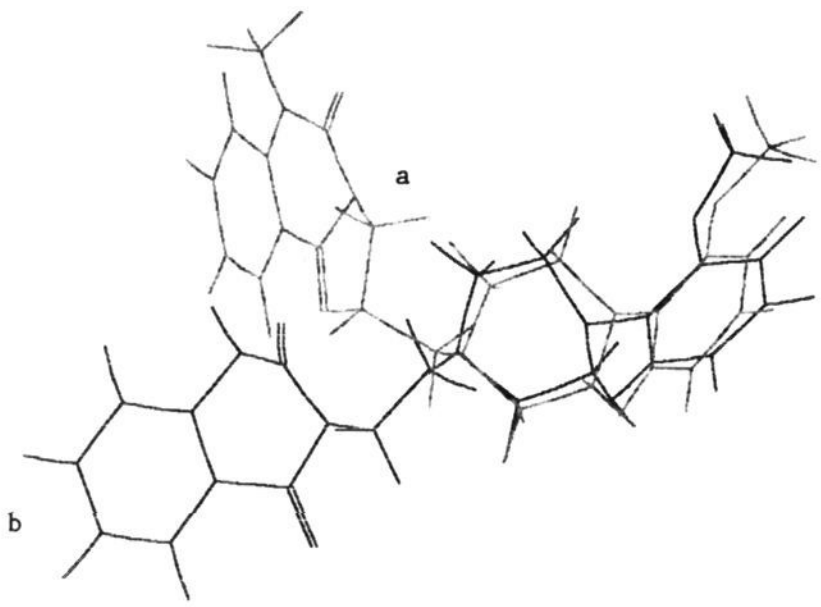


Figure 1. Superimposition of compound **20b** (a) and SGB-1534 (b) in the energy-minimized conformation state.

taining compounds represent the most potent compounds.[8] In general, these compounds showed the dose–response curves of the maximum changes in SBP, DBP, and heart rate after iv administration of each compound in rats, decreased both SBP and DBP and changed in heart rate (HR). However, these compounds decreased the BP immediately and reached a maximal effect in 10 min, and the antihypertensive activity of some compounds lasted for over 6 h. In spite of this, the antihypertensive potency in the 2-methoxy series (**20b** and **28b**) was better than that of 2-chloro series (**20c**, **26c**, and **28c**). In agreement, compounds **20b** and **28b** displayed a similar in vivo profile to SGB-1534 whereas compounds **25b–c**, **26b–c**, and **28c** showed no significant antihypertensive activity or high potency at the onset but short duration, in spite of their potent and highly selective affinity to the α_1-adrenoceptor. The observed high potency at onset and short duration with moderate efficacy for compounds **26b–c** and **28c** could be explained either by the high lipophilic property of the imidazo[1,2-*c*]quinazoline ring moiety or the unpredictable intrinsic factor of the compounds in vivo. These results show that imidazo[1,2-*c*]quinazolin-5(6*H*)-one with 4-(2-substituted phenyl)-1-piperazines have a long duration of antihypertensive action in SHR after intravenious administration and that modification of the imidazo[1,2-*c*]quinazolin-5(6*H*)-one moiety at 5-position influences in vivo performance.

In summary, the novel conformationally restricted analogues of ketanserin and SGB-1534 were prepared and show good to excellent anihypertensive activity in the SHR model. The presence of a substituent (methoxy or fluoro) at the 3- or 4-position of the phenyl ring at the 4-position of piperazine moiety dramatically reduced α_1-adrenoceptor affinity in vitro and antihypertensive activity in the SHR. The most potent compounds were those with the 2-methoxy substituent on the phenylpiperazine moiety and a methyl group at the N-6 position. Our study shows that the utility of conformationally restricted analogues of SGB-1534 having a methylene group separating the 2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one and piperazine moiety provides a potent α_1-antagonist. Evaluation of the side effect and pharmacological profile of these compounds is necessary for further development.

Experimental Section

General Methods. Melting points were obtained on an Electrothermal apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 983 G spectrophotometer. UV spectra were recorded on Becakman DU-50 spectrophometer. Infrared spectra were recorded on a Perkin-Elmer Model 983 G spectrophotometer. ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a either JEOL FX-100 or a JEOL JNM-EX400 spectrometer from National Taiwan Normal University or on a Bruker Model AM 300 spectrometer from National Taiwan University, Taipei, and are reported in parts per million with DMSO-d_6 as the internal standard on a δ scale. EI mass spectra was recorded on JEOL JMS-D100 mass spectrometer from National Taiwan University. Elemental analyses for C, H, and N were carried out either on a Heraeus Elemental Analyzer in Cheng-Kong University, Tainan, or on a Perkin-Elmer 240 Elemental Analyzer in National Taiwan University, Taipei, and were within ±0.4% of the theoretical values.

2-(3-Allylureido)benzonitrile (7). A mixture of anthranilonitrile (10.0 g, 85 mmol) and allyl isocyanate (7.5 mL, 85 mmol) was slightly heated to dissolve. The resulting solution was allowed to stir at room temperature for 2 days. The solid was collected by filtration and washed with ether (10 mL) to give **7** (14.4 g, 100%). An analytical sample was recrystallized from ethanol: mp 179–181 °C; IR (KBr) 3331, 3263, 2226 (CN), 1639 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.74 (p, 2H, CH_2), 5.09 (q, 1H, =CH), 5.17 (q, 1H, =CH), 5.86 (m, 1H, CH), 7.09 (t, 2H, Ar-H), 7.56 (t, 1H, Ar-H), 7.67 (d, 1H, Ar-H), 8.43 (d, 1H, Ar-H), 7.65 (d, 1H, NH), 8.54 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 41.47, 101.00, 114.97, 116.99, 120.61, 120.73, 122.22, 132.96, 133.83, 135.69, 142.66, 154.32. Anal. ($C_{11}H_{11}N_3O$) C, H, N.

3,4-Dihydro-4-imino-3-allylquinazolin-2(1*H*)-one (10). A mixture of **7** (10.0 g, 50 mmol) in ethanol (70 mL) and 28% ammonia water (50 mL) was heated on a steam bath with occasional stirring for 15 min. The mixture was then cooled to room temperature, and to the mixture was added water (100 mL). The solid was collected by filtration and was recrystallized from methanol with a few drops of ammonia water to give **10** (8.4 g, 84%): mp 223–224 °C; IR (KBr) 3284, 3203, 3147, 1691 (C=O), 1582 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.61 (d, 2H, =CH_2), 5.08 (q, 2H, CH_2), 5.85 (m, 1H, =CH), 7.07 (m, 2H, Ar-H), 7.46 (t, 1H, Ar-H), 8.04 (d, 1H, Ar-H), 8.85 (br s, 1H, NH), 10.74 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 42.54, 115.08, 115.81, 122.09, 126.13, 132.77, 133.15, 137.01, 149.76. Anal. ($C_{11}H_{11}N_3O$) C, H, N.

2-(Bromomethyl)-2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one (13). To a solution of **10** (10 g, 50 mmol) in tetrahydrofuran (70 mL) was added *N*-bromosuccinimide (9.0 g, 50 mmol). The mixture was then stirred at room temperature for 25 min. The solid was collected by filtration and recrystallized from THF to afford **13** (11.18 g, 95%): mp 213–214 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.67 (m, 2H, CH_2), 3.74 (q, 1H, CH), 3.94 (t, 1H, CH), 4.57 (m, 1H, =CH), 7.07 (q, 2H, Ar-H), 7.51 (t, 1H, Ar-H), 7.78 (d, 1H, Ar-H), 10.65 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 47.80, 64.16, 110.27, 115.13, 122.23, 125.80, 133.59, 139.97, 147.47, 153.98, 206.07. Anal. ($C_{11}H_{10}N_3OBr$) C, H, N.

2-[(4-Phenylpiperazin-1-yl)methyl]-2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one (16a). A mixture of **13** (0.5 g, 1.78 mmol) and *N*-phenylpiperazine (0.28 mL, 3.56 mmol) in acetonitrile (25 mL) was refluxed for 13 h. The hot mixture was filtered and washed with acetonitrile (10 mL) to give **16a** (490 mg, 76%). An analytical sample was prepared from a mixture of acetonitrile and methanol (1:1): mp 257–258 °C; UV λ_{max} nm ($\epsilon \times 10^4$) (methanol) 250 (1.3), 316 (0.4); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.43–2.73 (m, 7H, CH_2), 3.11 (t, 3H, CH_2), 3.65 (q, 1H, CH), 3.91 (t, 1H, CH), 4.41 (m, 1H, CH), 6.75 (t, 1H, Ar-H), 6.91 (d, 2H, Ar-H), 7.06 (q, 2H, Ar-H), 7.17 (q, 2H, Ar-H), 7.48 (p, 1H, Ar-H), 7.78 (d, 1H, Ar-H), 10.53 (s, 1H, NH); MS *m/z* 361 (M^+). Anal. ($C_{21}H_{23}N_5O$) C, H, N.

2-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one (16b) was obtained in 66% yield using a procedure similar to that which afforded **16a**: mp 226–227 °C; UV λ_{max} nm ($\epsilon \times 10^4$) (methanol) 250 (1.0), 278 (0.4), 317 (0.5); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.44–2.69 (m, 6H, 3 CH_2), 2.95 (br s, 4H, CH_2), 3.67 (q, 1H, CH), 3.76 (s, 3H, OCH_3), 3.87 (t, 1H, CH), 4.40 (m, 1H, CH), 6.88 (d, 4H, Ar-H), 7.06 (m, 2H, Ar-H), 7.48 (t, 1H, Ar-H), 7.78 (d, 1H, Ar-H), 10.50 (br s, 1H, NH); MS *m/z* 391 (M^+). Anal. ($C_{22}H_{25}N_5O_2$) C, H, N.

2-[[4-(2-Chlorophenyl)piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one (16c) was obtained in 67% yield using a procedure similar to that which afforded **16a**: mp 235–236 °C; UV λ_{max} nm ($\epsilon \times 10^4$) (methanol) 252 (1.3), 317 (0.6); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.41–2.84 (m, 6H, 3 CH_2), 2.92–3.02 (br s, 2H, CH_2), 3.07–3.31 (m, 2H, CH_2), 3.67–4.03 (m, 2H, CH_2), 4.22–4.28 (m, 1H, CH), 7.34–8.13 (m, 8H, Ar-H), 10.89 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 48.01, 50.93, 53.40, 62.91, 62.99, 111.28, 115.14, 120.85, 122.18, 123.81, 125.79, 127.62, 128.05, 130.30, 133.16, 139.99, 148.26, 149.05, 152.69; MS *m/z* 394 (M^+). Anal. ($C_{21}H_{22}N_5ClO$) C, H, N.

2-[[4-(3-Methoxyphenyl)piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one (16d) was obtained in 88% yield using a procedure similar to that which afforded **16a**, mp >300 °C. Anal. ($C_{22}H_{25}N_5O_2$) C, H, N.

2-[[4-(4-Methoxyphenyl)piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one (16e) was obtained in 54% yield using a procedure similar to that which afforded **16a**: mp 229–231 °C (CH_3CN); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.42–2.71 (m, 6H, 3 CH_2), 3.09 (m, 4H, 2 CH_2), 3.65 (m, 1H, CH), 3.69 (s, 3H, CH_3), 3.90 (m, 1H, CH), 4.41 (m, 1H, CH), 6.33–6.51 (m, 3H, Ar-H), 7.03–7.11 (m, 3H, Ar-H), 7.48 (t, 1H, Ar-H), 7.78 (d, 1H, Ar-H), 10.50 (s, 1H, NH); MS *m/z* 391 (M^+), 229, 205. Anal. ($C_{22}H_{25}N_5O_2$) C, H, N.

2-[[4-(4-Fluorobenzyl)piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one (16f) was obtained in 61% yield using a procedure similar to that which afforded **16a**, mp 248–249 °C. Anal. ($C_{21}H_{22}N_5FO$) C, H, N.

2-[(4-Benzylpiperazin-1-yl)methyl]-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one (16g) was obtained in 64% yield using a procedure similar to that which afforded **16a**: mp 222–224 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.50–3.00 (br s, 10H, CH_2), 3.74–3.80 (br s, 3H, CH_2), 4.04 (t, 1H, CH), 4.53 (m, 1H, CH), 6.99–7.10 (m, 2H, Ar-H), 7.24–7.41 (m, 6H, Ar-H), 7.90 (d, 1H, Ar-H), 9.15 (br s, 1H, NH). Anal. ($C_{22}H_{25}N_5O$) C, H, N.

2-[(4-Piperonylpiperazin-1-yl)methyl]-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one (16h) and 2-Methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one (19). A mixture of **13** (0.5 g, 1.78 mmol) and 1-piperonylpiperazine (0.78 g, 3.56 mmol) in CH_3CN (25 mL) was refluxed for 17 h. The solvent was then removed in vacuo to the oily residue. The residue was purified by column chromatography [silica gel, 25 g; column diameter, 2.5 cm; solvent system, chloroform/ethyl acetate (9/1)] to furnish **16h** (620 mg, 67%) and **19** (90 mg, 22%). Compound **16h**: mp 236–238 °C. Anal. ($C_{23}H_{23}N_5O_3/H_2O/HBr$) C, H, N. Compound **19**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.32 (s, 3H, CH_3), 7.27 (t, 1H, Ar-H), 7.35 (d, 1H, Ar-H), 7.57 (s, 1H, Ar-H), 8.10 (d, 1H, Ar-H). Anal. ($C_{11}H_9N_3O$) C, H, N.

2-[[4-(2-Pyridinyl)piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one (16i) was obtained in 81% yield using a procedure similar to that which afforded **16a**: mp 242–243 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.65–2.83 (br s, 6H, CH_2), 3.59 (br s, 4H, CH_2), 3.91 (q, 1H, CH), 4.09 (t, 1H, CH), 4.57 (m, 1H, CH), 6.62 (t, 2H, Ar-H), 6.98 (d, 1H, Ar-H), 7.11 (t, 1H, Ar-H), 7.45 (q, 2H, Ar-H), 7.95 (d, 1H, Ar-H), 8.17 (d, 1H, Ar-H), 9.04 (br s, 1H, NH). Anal. ($C_{20}H_{22}N_6O$) C, H, N.

2-[[1-(4-Chlorobenzhydryl)piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one (16j) was obtained in 40% yield using a procedure similar to that which afforded **16a**: mp 245–246 °C (CH_3CN); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29–2.57 (m, 10H, CH_2), 3.29 (m, 1H, CH), 3.59 (m, 1H, CH), 3.84 (t, 1H, CH), 4.31 (s, 2H, CH_2), 7.01–7.75 (m, 13 H, Ar-H), 10.50 (br s, 1H, NH). Anal. ($C_{23}H_{25}N_5ClO$) C, H, N.

8-[[2,3,5,6-Tetrahydro-5-oxoimidazo[1,2-c]quinazolin-2-yl]methyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (16k) was obtained in 74% yield using a procedure similar to that which afforded **16a**: mp 250–251 °C (CH_3CN); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (q, 2H, CH_2), 2.44–2.64 (m, 4H, 2 CH_2), 2.78–2.89 (m, 4H, 2 CH_2), 3.71–3.77 (m, 1H, CH), 3.96 (m, 1H, CH), 4.37 (m, 1H, CH), 4.55 (s, 2H, CH_2), 6.71–6.82 (m, 3H, Ar-H), 7.06 (t, 2H, Ar-H), 7.22 (t, 2H, Ar-H), 7.46 (t, 1H, Ar-H), 7.77 (d, 1H, Ar-H), 8.59 (s, 1H, NH), 10.54 (s, 1H, NH). Anal. ($C_{24}H_{26}N_6O_2 \cdot {}^1/_4H_2O$) C, H, N.

2-[[4-(4-Fluorobenzoyl)piperidin-1-yl]methyl]-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one (16l) was obtained in 81% yield using a procedure similar to that which afforded **16a**: mp 220–221 °C (acetone); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.51–1.73 (m, 4H, 2 CH_2), 2.10–2.42 (m, 5H, 2 CH_2 + CH), 2.87 (d, 1H, CH), 3.06 (d, 1H, CH), 3.36 (m, 1H, CH), 3.62 (m, 1H, CH), 3.88 (m, 1H, CH), 4.37 (m, 1H, CH), 7.06 (m, 2H, Ar-H), 7.33 (m, 2H, Ar-H), 7.76 (d, 1H, Ar-H), 8.04 (m, 2H, Ar-H), 10.50 (s, 1H, NH). Anal. ($C_{23}H_{23}N_4FO_2$) C, H, N.

3-[[2,3,5,6-Tetrahydro-5-oxoimidazo[1,2-c]quinazolin-2-yl]methyl]azaspiro[5.5]undecane (16m) was obtained in 73% yield using a procedure similar to that which afforded **16a**: mp 203–205 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.27 (s, 4H, CH_2), 1.34 (s, 6H, CH_2), 2.28 (d, 2H, CH_2), 2.48 (d, 2H, CH_2), 3.39 (m, 7H, CH_2), 3.85 (t, 1H, CH), 4.34 (m, 1H, CH), 7.03 (m, 2H, Ar-H), 7.47 (t, 1H, Ar-H), 7.74 (d, 1H, Ar-H), 10.54 (s, 1H, NH); MS *m/z* 166 (M^+). Anal. ($C_{21}H_{23}N_4O$) C, H, N.

2-[[(1-Benzylpiperidin-4-yl)amino]methyl]-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one (16n) was obtained in 76% yield using a procedure similar to that which afforded **16a**, mp 206–208 °C. Anal. ($C_{23}H_{27}N_5O$) C, H, N.

2-[(4-Benzylpiperidin-1-yl)methyl]-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one (16o) was obtained in 62% yield using a procedure similar to that which afforded **16a**: mp 225–227 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.56–1.66 (br s, 5H, CH_2), 2.21–2.33 (br s, 2H, CH_2), 2.54 (br s, 2H, CH), 2.75 (br s, 1H, CH), 2.90 (br s, 1H, CH), 3.09 (br s, 1H, CH), 3.29 (br s, 1H, CH), 3.80 (q, 1H, CH), 4.06 (t, 1H, CH), 4.60 (m, 1H, CH), 6.99–7.29 (m, 7H, Ar-H), 7.39 (t, 1H, Ar-H), 7.89 (d, 1H; Ar-H), 9.49 (br s, 1H, NH). Anal. ($C_{23}H_{25}N_4O$) C, H, N.

3,4-Dihydro-4-imino-3-allylquinazoline-2(1H)-thione (11). A mixture of anthranilonitrile (10.0 g, 85 mmol) and allyl isothiocyanate (15 mL, 151 mmol) was slightly heated to dissolve. The resulting solution was allowed to stir at room temperature for 5 days. The solid was collected by filtration, washed with acetonitrile (10 mL), and recrystallized from ethanol to give **11** (8.05 g, 44%): mp 168–169 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.07–5.25 (m, 4H, =CH_2 + CH_2), 5.75–6.06 (m, 1H, =CH), 7.13–7.63 (m, 3H, Ar-H), 8.05–8.13 (d, 1H, Ar-H), 9.40 (s, 1H, NH), 12.13 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 48.43, 115.56, 116.63, 123.92, 125.96, 132.20, 133.04, 135.59, 174.38; MS *m/z* 217 (M^+), 201, 183, 160. Anal. ($C_{11}H_{11}N_3S$) C, H, N.

2-(Bromomethyl)-2,3-dihydroimidazo[1,2-c]quinazoline-5(6H)-thione (14). To a solution of **11** (5.5 g, 25.31 mmol) in acetonitrile (60 mL) was added *N*-bromosuccinimide (6.0 g, 33.52 mmol). The mixture was then stirred at room temperature for 50 min. The solid was collected by filtration and recrystallized from a mixture of acetonitrile and methanol to afford **14** (3.01 g, 40%): mp >300 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.90 (m, 2H, CH_2), 4.54–4.73 (m, 3H, CH and CH_2), 7.66–7.71 (t, 2H, Ar-H), 7.97–9.02 (m, 1H, Ar-H), 8.54 (d, 1H, Ar-H), 9.80 (s, 1H, NH), 10.50 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 47.80, 64.16, 110.27, 115.13, 122.23, 125.80, 133.59, 139.97, 147.47, 153.98, 206.07; MS *m/z* 296 (M^+), 295 ($M^+ - 1$), 216 ($M^+ - 80$), 202 ($M^+ - 94$). Anal. ($C_{11}H_{10}N_3SBr \cdot HBr$) C, H, N.

2-[(4-Phenylpiperazin-1-yl)methyl]-2,3-dihydroimidazo[1,2-c]quinazoline-5(6H)-thione (17). A mixture of **14** (3.0 g, 10.13 mmol), *N*-phenylpiperazine (2.5 mL, 15.41 mmol), and sodium bicarbonate (1.7 g, 20.24 mmol) in acetonitrile (70 mL) was refluxed for 24 h. The hot mixture was filtered and washed with acetonitrile (10 mL) to give **17** (490 mg, 76%). An analytical sample was prepared from a mixture of acetonitrile and methanol (1:1): mp 257–258 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.43–2.73 (m, 7H, CH_2), 3.11 (t, 3H, CH_2), 3.65 (q, 1H, CH), 3.91 (t, 1H, CH), 4.41 (m, 1H, CH), 6.75 (t, 1H, Ar-H), 6.91 (d, 2H, Ar-H), 7.06 (q, 2H, Ar-H), 7.17 (q, 2H, Ar-H), 7.48 (p, 1H, Ar-H), 7.78 (d, 1H, Ar-H), 10.53 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 29.43, 48.14, 51.91, 52.67, 61.18, 115.33, 118.75, 124.75, 124.92, 125.60, 128.81, 132.41, 145.39, 150.86, 159.50, 179.22; MS *m/z* 361 (M^+). Anal. ($C_{21}H_{23}N_5S$) C, H, N.

3,4-Dihydro-3-allyl-4-imino-6,7-dimethoxyquinazolin-2(1H)-one (12) was prepared in 72% yield using a similar procedure which afforded **11**. An analytical sample was recrystallized from ethanol: mp 283–284 °C; IR (KBr) 3380, 3295, 3127, 1664 (C=O), 1626 cm^{-1}; ^{1}H NMR (100 MHz, DMSO-d_6) δ 3.78 (s, 6H, 2 CH_3), 4.62 (d, 2H, J = 4.8 Hz, CH_2), 5.05 (d, 2H, = 12.8 Hz, CH_2), 5.94–6.03 (m, 1H, CH), 6.62 (s, 1H, Ar-H), 7.54 (s, 1H, Ar-H); MS *m/z* 260 ($M^+ - 1$), 246 ($M^+ - 15$), 230 ($M^+ - 31$), 216 ($M^+ - 45$), 206 ($M^+ - 55$). Anal. ($C_{13}H_{15}N_3O$) C, H, N.

2-(Bromomethyl)-8,9-dimethoxy-2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one (15) was prepared in 92% yield uising a similar procedure which afforded **13**. An analytical sample was recrystallized from ethanol: mp 223–224 °C; IR (KBr) 3196, 3081, 1669 (C=O), 1603 cm^{-1}; ^1H NMR (100 MHz, DMSO-d_6) δ 3.78 (s, 3H, CH_3), 3.83 (s, 3H, CH_3), 3.78–4.21 (m, 4H, 2 CH_2), 6.68 (s, 1H, Ar-H), 7.32 (s, 1H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 47.87, 55.61, 55.68, 64.44, 98.12, 102.14, 106.63, 135.31, 144.84, 147.77, 153.64, 153.85; MS *m/z* 341 (M^+), 259 (M^+ – 82), 246 (M^+ – 95). Anal. ($C_{13}H_{14}N_3BrO_3$) C, H, N.

2-[(4-Phenylpiperazin-1-yl)methyl]-8,9-dimethoxy-2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one (18) was obtained in 90% yield using a procedure similar to that which afforded **16a**. An analytical sample was recrystallized from ethanol: mp 283–284 °C; ^1H NMR (100 MHz, DMSO-d_6 + 1 N D_2SO_4) δ 3.37 (br s, 8H, 4 CH_2), 3.81 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 3.62–4.20 (m, 3H, CH_2 + CH), 4.46 (t, 1H, CH), 4.95 (br s, 1H, CH), 6.79 (s, 1H, Ar-H), 6.82–7.23 (m, 5H, Ar-H), 7.56 (s, 1H, Ar-H); ^{13}C NMR (25 MHz, DMSO-d_6 + 1 N D_2SO_4) δ 46.35, 49.70, 52.15, 52.50, 56.78, 57.19, 58.82, 96.33, 98.55, 107.05, 116.66, 121.11, 130.22, 141.02, 146.02, 146.66, 148.53, 158.37, 158.55; MS *m/z* 421 (M^+), 303 (M^+ – 118), 289 (M^+ – 132), 275 (M^+ – 146). Anal. ($C_{23}H_{27}N_5O_3$) C, H, N.

2-[(4-Phenylpiperazin-1-yl)methyl]-6-methyl-2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one (20a). To a solution of **16a** (1.0 g, 2.8 mmol) in DMF (30 mL) was added 50% sodium hydride (0.27 g, 5.6 mmol). The solution was stirred under an ice-cooling bath for 20 min, and then to the solution was added methyl iodide (0.21 mL, 3.36 mmol). The resulting soultion was stirred for 24 hours, and the mixture was poured into ice water (100 mL) to get precipitates which were collected by filtration to give **20a** (0.8 g, 76%). An analytical sample was recrystallized from acetonitrile: mp 185–186 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.41–2.75 (m, 6H, 3 CH_2), 3.11 (m, 4H, 2 CH_2), 3.39 (s, 3H, CH_3), 3.84–3.88 (m, 1H, CH), 3.99–4.04 (m, 1H, CH), 4.37–4.45 (m, 1H, CH), 6.76 (t, 1H, J = 7.3 Hz, Ar-H), 6.84 (d, 2H, J = 8.3 Hz, Ar-H), 6.99 (d, 1H, J = 8.3 Hz, Ar-H), 7.08 (t, 1H, J = 7.8 Hz, Ar-H), 7.18 (m, 2H, Ar-H), 7.46 (t, 1H, J = 7.3 Hz, Ar-H), 7.97 (d, 1H, J = 7.9 Hz, Ar-H); ^{13}C NMR (100.40 MHz, $CDCl_3$) δ 29.69, 49.62, 53.79, 63.38, 112.86, 113.87, 115.97, 119.56, 122.67, 126.88, 129.01, 133.42, 140.88, 148.96, 151.27, 152.88; MS *m/z* 361 (M^+). Anal. ($C_{23}H_{25}N_5O$) C, H, N.

2-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-6-methyl-2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one (20b) was prepared in 85% yield using a similar procedure which afforded **20a**. An analytical sample was recrystallized from acetonitrile: mp 157–158 °C; UV λ_{max} nm ($\epsilon \times 10^4$) (methanol) 252 (0.8), 320 (0.8); ^1H NMR (300 MHz, DMSO-d_6) δ 2.40–2.72 (m, 6H, 3 CH_2), 2.96 (br s, 2H, 2 CH_2), 3.36 (s, 3H, CH_3), 3.69–3.74 (m, 1H, CH), 3.77 (s, 3H, CH_3), 3.96 (t, 1H, J = 10.5 Hz, CH), 4.40 (m, 1H, CH), 6.90 (m, 4H, Ar-H), 7.19 (t, 1H, J = 7.6 Hz, Ar-H), 7.27 (1H, J = 8.5 Hz, Ar-H), 7.62 (t, 1H, J = 7.8 Hz, Ar-H), 7.89 (d, 1H, J = 6.2 Hz, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 29.83, 49.62, 50.50, 53.90, 55.67, 63.02, 63.39, 112.2, 112.7, 115.05, 118.28, 121.21, 122.73, 122.83, 126.35, 133.90, 141.08, 141.62, 148.67, 152.18, 152.35; MS *m/z* 405 (M^+). Anal. ($C_{23}H_{27}N_5O_2$) C, H, N.

2-[[4-(2-Chlorophenyl)piperazin-1-yl]methyl]-6-methyl-2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one (20c) was prepared in 63% yield using a similar procedure which afford **20a**. An analytical sample was recrystallized from acetonitrile: mp 165–166 °C; UV λ_{max} nm ($\epsilon \times 10^4$) (methanol) 253 (1.3), 319 (0.4); ^1H NMR (400 MHz, $CDCl_3$) δ 2.51 (dd, 1H, J = 8.8 Hz, J = 3.9 Hz, CH), 2.67 (m, 2H, CH_2), 2.79 (m, 3H, CH_2 + CH), 3.19 (m, 4H, 2 CH_2), 3.47 (s, 3H, CH_3), 3.93 (m, 1H, CH), 4.10 (m, 1H, CH), 4.49 (m, 1H, CH), 6.91 (t, 1H, J = 8.3 Hz, Ar-H), 7.08 (t, 1H, J = 8.3 Hz, Ar-H), 7.15 (d, 1H, J = 7.8 Hz, Ar-H), 7.19 (m, 1H, Ar-H), 7.26 (t, 2H, J = 7.3 Hz, Ar-H), 7.55 (t, 1H, J = 7.3 Hz, Ar-H), 8.05 (d, 1H, J = 7.8 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.72, 49.15, 49.66, 53.83, 63.36, 112.90, 113.91, 116.03, 119.61, 122.74, 126.87, 129.04, 133.46, 140.93, 149.02, 151.30, 152.95. Anal. ($C_{22}H_{24}N_5ClO$) C, H, N.

Quinazoline-2,4(1*H*,3*H*)-dithione (21). A mixture of anthranilonitrile (3.0 g, 25.4 mmol) and carbon disulfide (10 mL, 0.13 mole) in pyridine (10 mL) was refluxed for 8 h. After the mixture was cooled to room temperature for 1 h, ethanol (150 mL) was added to the mixture. The yellowish solid was then collected by filtration and washed with ether (15 mL) to afford **21** (4.53 g, 92%): mp 334–337 °C [lit.[15 mp] 335–338 °C]; ^1H NMR (100 MHz, DMSO-d_6) δ 7.23–7.37 (m, 2H, Ar-H), 7.65–7.81 (m, 1H, Ar-H), 8.23–8.33 (m, 1H, Ar-H), 13.05 (s, 2H, NH_2, D_2O exchangeable); ^{13}C NMR (25 MHz, DMSO-d_6) δ 116.02, 122.52, 125.04, 129.90, 135.82, 136.11, 170.21, 187.57.

2,4-Dimethylthioquinazoline (22). To a solution of **21** (10 g, 51.5 mmol) in 10% aqueous sodium hydroxide solution (50 mL) was added methyl iodide (10 mL, 0.1 mol) dropwise. After the mixture was stirred at room temperature for 24 h, the white solid was collected by filtration and washed with water (10 mL) to furnish **22** (10.65 g, 93%): mp 85 °C; ^1H NMR (100 MHz, DMSO-d_6) δ 2.61 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 7.53–7.82 (m, 4H, Ar-H); ^{13}C NMR (25 MHz, DMSO-d_6) δ 12.13, 13.71, 120.23, 123.45, 126.03, 126.56, 134.30, 147.60, 165.78, 170.50; MS *m/z* 221 (M^+ – 1), 206 (M^+ – 15), 188 (M^+ – 60), 159 (M^+ – 62). Anal. ($C_{10}H_{10}N_2S_2$) C, H, N.

4-Allyl-2-(methylthio)quinazoline (23). A mixture of **22** (10 g, 45 mmol) and allylamine (68 mL, 0.9 mol) in acetonitrile (200 mL) was heated in a stainless vessel at 120–130 °C for 48 h. The mixture was concentrated in vacuo to 20 mL at 50 °C and was then allowed to set in a refrigerator for 6 h. The solid was collected by filtration and washed with acetonitrile (10 mL) to give **23** (9.47 g, 91%). An analytical sample was recrystallized from ethyl acetate: mp 133–135 °C; ^1H NMR (100 MHz, DMSO-d_6) δ 2.50 (s, 3H, CH_3), 4.16 (t, 2H, J = 6.0 Hz, CH_2), 5.02–5.26 (m, 2H, CH_2), 5.76–6.18 (m, 1H, Ar-H), 7.26–7.74 (m, 3H, Ar-H), 8.18 (d, 1H, J = 8.5 Hz, Ar-H), 8.50 (, t, 1H, J = 5.9 Hz, NH, D_2O exchangeable); ^{13}C NMR (25 MHz, DMSO-d_6) δ 13.48, 42.77, 112.67, 115.49, 122.75, 124.10, 125.74, 132.71, 134.65, 149.30, 158.20, 166.37; MS *m/z* 231 (M^+), 205 (M^+ – 26), 183 (M^+ – 48). Anal. ($C_{12}H_{13}N_3S$) C, H, N.

3-(Bromomethyl)-5-(methylthio)-2,3-dihydroimidazo[1,2-*c*]quinazoline (24). To a suspension of **23** (10 g, 43 mmol) in acetonitrile (50 mL) was added NBS (9 g, 50 mmol), and the mixture turned into a solution. The solution was then stirred at room temperature. After 10 min, the white solid gradually formed and became a suspension again. The reaction was complete within 3 h. The solid was then collected by filtration and washed with CH_3CN (10 mL) to give **24** (11.75 g, 85%). An analytical sample was recrystallized from acetonitrile: mp 162–163 °C; ^1H NMR (100 MHz, DMSO-d_6) δ 2.78 (s, 3H, CH_3), 4.00–4.43 (m, 4H, 2 CH_2), 5.45–5.49 (m, 1H, CH), 7.68–7.73 (m, 1H, Ar-H), 7.80 (d, 1H, Ar-H), 8.06 (t, 1H, Ar-H), 8.38 (d, 1H, Ar-H); ^{13}C NMR (25 MHz, DMSO-d_6) δ 13.02, 35.80, 57.37, 59.08, 116.77, 124.98, 125.36, 125.48, 133.06, 145.75, 152.63, 153.69; MS *m/z* 310 (M^+), 309 (M^+ – 1), 230 (M^+ – 80), 174 (M^+ – 136). Anal. ($C_{12}H_{12}N_3SBr$) C, H, N.

3-[(4-Phenylpiperazin-1-yl)methyl]-5-(methylthio)-2,3-dihydroimidazo[1,2-*c*]quinazoline (25a). A mixture of **24** (3.0 g, 9.7 mmol) and 1-phenylpiperazine (3.0 mL, 18.5 mmol) in acetonitrile (60 mL) was refluxed using an oil bath for 24 h. The mixture was then concentrated in vacuo to 30 mL at 40 °C. The white solid was collected by filtration and washed with water (25 mL) to give **25a** (2.13 g, 56%). An analytical sample was recrystallized from CH_3CN: mp 133–134 °C; UV λ_{max} nm ($\epsilon \times 10^4$) (methanol) 246 (1.1); ^1H NMR (400 MHz, DMSO-d_6) δ 2.50–2.56 (m, 4H, 2 CH_2), 2.59 (s, 3H, CH_3), 2.68–2.75 (m, 2H, CH_2), 3.09–3.13 (m, 4H, 2 CH_2), 3.92–4.09 (m, 2H, CH_2), 4.51 (m, 1H, CH), 6.76 (t, J = 7.3 Hz, 1H, Ar-H), 6.89 (d, J = 7.8Hz, 2H, Ar-H), 7.17–7.26 (m, 3H, Ar-H), 7.33 (d, J = 7.8 Hz, 1H, Ar-H), 7.56 (t, J = 7.8 Hz, 1H, Ar-H), 7.84 (d, J = 7.8 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.96, 48.02, 52.96, 55.87, 58.68, 59.14, 115.19, 116.79, 118.58, 124.63, 124.94, 125.27, 128.67, 132.64, 145.86, 150.76, 152.26, 153.95; MS *m/z* 391 (M^+), 344 (M^+ – 47), 259 (M^+ – 132), 216 (M^+ – 175), 175 (M^+ – 216, 100), 132 (M^+ – 259). Anal. ($C_{22}H_{28}N_5S$) C, H, N.

3-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-5-(methylthio)-2,3-dihydroimidazo[1,2-*c*]quinazoline (25b) was prepared in 82% yield using a procedure similar to that of **25a**. An analytical sample was recrystallized from CH_3CN: mp 174–175 °C; UV λ_{max} nm ($\epsilon \times 10^4$) (methanol) 285 (0.7), 309 (0.8); ^1H NMR (400 MHz, DMSO-d_6) δ 2.43–2.56 (m, 4H, 2 CH_2), 2.59 (s, 3H, SCH_3), 2.86–2.87 (m, 2H, CH_2), 2.96 (m, 4H, 2 CH_2), 3.77 (s, 3H, OCH_3), 3.91–4.09 (m, 2H, CH_2), 4.52 (m, 1H, CH), 6.87 (s, 2H, Ar-H), 6.92 (s, 2H, Ar-H), 7.25 (t, J = 7.3 Hz, 1H, Ar-H), 7.33 (d,

J = 7.3 Hz, 1H, Ar-H), 7.55 (t, J = 6.8 Hz, 1H, Ar-H), 7.83 (d, J = 7.3 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.91, 49.81, 53.33, 55.21, 55.87, 58.67, 59.29, 112.05, 116.75, 117.77, 120.70, 122.11, 124.58, 124.91, 125.23, 132.60, 141.11, 145.83, 151.88, 152.23, 153.96; MS m/z 422 (M^+), 374 (M^+ - 48), 205 (M^+ - 217, 100). Anal. ($C_{23}H_{27}N_5SO$) C, H, N.

3-[[4-(2-Chlorophenyl)piperazin-1-yl]methyl]-5-(methylthio)-2,3-dihydroimidazo[1,2-c]quinazoline (25c) was prepared in 45% yield using a procedure similar to that of **25a**. An analytical sample was recrystallized from ethanol: mp 184–185 °C; UV λ_{max} nm ($\epsilon \times 10^4$) (methanol) 248 (1.4), 309 (0.7); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17–2.54 (m, 2H, CH_2), 2.56 (s, 3H, SCH_3), 2.58–2.82 (m, 4H, 2 CH_2), 2.96–3.02 (m, 4H, 2 CH_2), 4.05–4.07 (m, 2H, CH_2), 4.4.36–4.37 (m, 1H, CH), 6.86–7.89 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.50, 51.09, 53.81, 56.43, 59.28, 59.68, 117.05, 120.32, 123.64, 125.10, 125.30, 125.74, 127.51, 128.72, 130.57, 132.89, 146.53, 149.17, 153.81, 154.27. Anal. ($C_{22}H_{24}N_5ClS$) C, H, N.

3-[[4-(3-Methoxyphenyl)piperazin-1-yl]methyl]-5-(methylthio)-2,3-dihydroimidazo[1,2-c]quinazoline (25d) was prepared in 57% yield using a procedure similar to that of **25a**. An analytical sample was recrystallized from acetonitrile: mp 138–139 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.50–256 (m, 2H, CH_2), 2.59 (s, 3H, SCH_3), 2.67–2.74 (m, 4H, 2 CH_2), 3.11 (m, 4H, 2 CH_2), 3.70 (s, 3H, OCH_3), 3.91–4.05 (m, 2H, CH_2), 4.51 (m, 1H, CH), 6.35 (d, J = 7.8 Hz, 1H, Ar-H), 6.43 (s, 1H, Ar-H), 6.49 (d, J = 8.3 Hz, 1H, Ar-H), 7.09 (t, J = 8.3 Hz, 1H, Ar-H), 7.24 (t, J = 7.8 Hz, 1H, Ar-H), 7.33 (d, J = 8.3 Hz, 1H, Ar-H), 7.54 (t, J = 7.8 Hz, 1H, Ar-H), 7.83 (d, J = 7.8 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.96, 47.99, 52.94, 54.68, 55.87, 58.68, 59.12, 101.42, 103.97, 107.88, 116.77, 124.63, 124.94, 125.27, 129.35, 132.64, 145.85, 152.12, 152.25, 153.95, 160.07; MS m/z 422 (M^+), 374 (M^+ - 48), 259 (M^+ - 163), 205 (M^+ - 217, 100). Anal. ($C_{23}H_{27}N_5SO$) C, H, N.

3-[[4-(4-Methoxyphenyl)piperazinyl]methyl]-5-(methylthio)-2,3-dihydroimidazo[1,2-c]quinazoline (25e) was prepared in 54% yield using a procedure similar to that of **25a**. An analytical sample was recrystallized from acetonitrile: mp 133–135 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.51–2.57 (m, 4H, 2 CH_2), 2.60 (s, 3H, SCH_3), 2.72–2.75 (m, 2H, CH_2), 2.99 (m, 4H, 2 CH_2), 3.68 (s, 3H, OCH_3), 3.91–4.03 (m, 2H, CH_2), 4.51 (m, 1H, CH), 6.83 (m, 4H, Ar-H), 7.24 (t, J = 7.3 Hz, 1H, Ar-H), 7.33 (d, J = 7.8 Hz, 1H, Ar-H), 7.54 (t, J = 6.8 Hz, 1H, Ar-H), 7.83 (d, J = 6.8 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.91, 49.38, 53.07, 55.05, 55.89, 58.65, 59.12, 114.13, 116.77, 117.11, 124.59, 124.89, 125.23, 132.59, 145.19, 145.83, 152.23, 152.78, 153.91; MS m/z 421 (M^+), 406 (M^+ - 15), 373 (M^+ - 48), 259 (M^+ - 162), 216 (M^+ - 205), 205 (M^+ - 207, 100), 162 (M^+ - 259). Anal. ($C_{23}H_{27}N_5SO$) C, H, N.

3-[(4-Phenylpiperazin-1-yl)methyl]-5-methoxy-2,3-dihydroimidazo[1,2-c]quinazoline (26a). Compound **25a** (0.57 g, 1.46 mmol) was suspended in a 1 N ethanolic sodium hydroxide solution (25 mL). It was heated to 55 °C using an oil bath. After 48 h, the mixture was cooled to room temperature. The solid was then collected by filtration and was washed with water (30 mL) to afford **26a** (0.41 g, 75%). An analytical sample was recrystallized from CH_3CN: mp 146-147 °C; UV λ_{max} nm ($\epsilon \times 10^4$) (methanol) 250 (1.9), 283 (0.6), 315 (0.4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51–2.78 (m, 6H, 3 CH_2), 3.14–3.18 (m, 4H, 2 CH_2), 4.03 (s, 3H, CH_3), 4.06–4.19 (m, 2H, CH_2), 4.47–4.53 (m, 1H, CH), 6.85 (t, J = 7.3 Hz, 1H, Ar-H), 6.91 (d, J = 8.3 Hz, 2H, Ar-H), 7.18 (t, J = 7.3 Hz, 1H, Ar-H), 7.26 (t, J = 7.8 Hz, 1H, Ar-H), 7.34 (d, J = 7.8 Hz, 1H, Ar-H), 7.49 (t, J = 8.3 Hz, 1H, Ar-H), 7.96 (d, J = 6.9 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.07, 53.70, 54.52, 55.26, 59.43, 60.49, 116.01, 116.56, 119.67, 124.18, 125.26, 125.32, 129.05, 132.91, 147.35, 151.18, 152.04, 155.44; MS m/z 375 (M^+). Anal. ($C_{22}H_{25}N_5O$) C, H, N.

3-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-5-methoxy-2,3-dihydroimidazo[1,2-c]quinazoline (26b) was obtained in 60% yield using a procedure similar to that of **26a**. An anlytical sample was recrystallized from CH_3CN: mp 171–172 °C; UV λ_{max} nm ($\epsilon \times 10^4$) (methanol) 249 (1.0), 282 (0.5); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.47–272 (m, 6H, 3 CH_2), 2.94 (m, 4H, 2 CH_2), 3.77 (s, 3H, OCH_3), 3.85–4.07 (m, 2H, CH_2), 3.96 (s, 3H, OCH_3), 4.57–4.59 (m, 1H, CH), 6.86 (s, 2H, Ar-H), 6.91 (s, 2H, Ar-H), 7.19 (t, 1H, J = 7.7 Hz, Ar-H), 7.27 (d, 1H, J = 8.1 Hz, Ar-H), 7.52 (t, J = 7.2 Hz, Ar-H), 7.82 (d, 1H, J = 7.7 Hz, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 50.02, 53.47, 54.55, 54.64, 55.28, 58.89, 60.15, 111.89, 116.40, 117.88, 120.81, 122.33, 123.90, 124.94, 125.02, 132.81, 141.16, 147.05, 151.94, 152.17, 153.67; MS m/z 404 (M^+ - 1). Anal. ($C_{23}H_{27}N_5O_2$) C, H, N.

3-[[4-(2-Chlorophenyl)piperazin-1-yl]methyl]-5-methoxy-2,3-dihydroimidazo[1,2-c]quinazoline (26c) was obtained in 84% yield using a procedure similar to that of **26a**. An anlytical sample was recrystallized from CH_3CN: mp 148–149 °C; UV λ_{max} nm ($\epsilon \times 10^4$) (methanol) 250 (2.3), 281 (1.0), 314 (0.6); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.50–2.69 (m, 6H, 3 CH_2), 2.96 (m, 4H, 2 CH_2), 3.86–4.08 (m, 2H, CH_2), 3.96 (s, 3H, OCH_3), 4.57 (m, 1H, CH), 7.02 (t, J = 7.8 Hz, 1H, Ar-H), 7.14 (d, J = 7.8 Hz, 1H, Ar-H), 7.19 (t, J = 7.4 Hz, 1H, Ar-H), 7.27 (d, J = 8.3 Hz, 2H, Ar-H), 7.38 (d, J = 7.8 Hz, 1H, Ar-H), 7.51 (t, J = 7.4 Hz, 1H, Ar-H), 7.82 (d, J = 7.8 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 50.80, 53.33, 54.55, 54.62, 58.87, 60.02, 116.40, 120.83, 123.81, 123.90, 124.96, 125.02, 127.58, 128.03, 130.26, 132.81, 147.05, 148.94, 152.15, 153.67. Anal. ($C_{22}H_{24}N_5OCl$) C, H, N.

3-[[4-(3-Methoxyphenyl)piperazin-1-yl]methyl]-5-methoxy-2,3-dihydroimidazo[1,2-c]quinazoline (26d) was obtained in 90% yield using a procedure similar to that of **26a**. An anlytical sample was recrystallized from CH_3CN: mp 99–100 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.51–2.62 (m, 6H, 3 CH_2), 3.09 (m, 4H, 2 CH_2), 3.70 (s, 3H, CH_3), 3.95 (s, 3H, CH_3), 3.87–4.03 (m, 2H, CH_2), 4.54 (m, 1H, CH), 6.35 (d, J = 8.3 Hz, 1H, Ar-H), 6.43 (s, 1H, Ar-H), 6.49 (d, J = 8.3 Hz, 1H, Ar-H), 7.09 (t, J = 8.3 Hz, 1H, Ar-H), 7.19 (t, J = 7.8 Hz, 1H, Ar-H), 7.27 (d, J = 8.3 Hz, 1H, Ar-H), 7.51 (t, J = 7.8 Hz, 1H, Ar-H), 7.82 (d, J = 7.3 Hz, 1H, Ar-H).; 7.84 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 48.13, 53.11, 54.53, 54.66, 54.79, 58.90, 59.98, 101.44, 104.02, 107.99, 116.42, 123.88, 124.94, 124.99, 129.53, 132.77, 147.05, 152.14, 152.28, 153.67, 160.15; MS m/z 405 (M^+), 270 (M^+ - 135), 243 (M^+ - 162), 205 (M^+ - 200, 100). Anal. ($C_{23}H_{27}N_5O_2$) C, H, N.

3-[[4-(4-Methoxyphenyl)piperazin-1-yl]methyl]-5-methoxy-2,3-dihydroimidazo[1,2-c]quinazoline (26e) was obtained in 90.4% yield using a procedure similar to that of **26a**. An anlytical sample was recrystallized from CH_3CN mp 149–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21–2.76 (m, 6H, 3 CH_2), 3.06–3.08 (m, 4H, 2 CH_2), 3.76 (s, 3H, CH_3), 4.03 (s, 3H, CH_3), 4.05–4.19 (m, 2H, CH_2), 4.48–4.53 (m, 1H, CH), 6.86 (m, 4H, Ar-H), 7.18 (t, J = 7.8 Hz, 1H, Ar-H), 7.34 (d, J = 7.8 Hz, 1H, Ar-H), 7.49 (t, J = 8.3 Hz, 1H, Ar-H), 7.96 (d, J = 7.8 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.57, 53.83, 54.54, 55.29, 55.51, 59.39, 60.49, 114.38, 118.15, 124.20, 125.28, 125.35, 132.93, 145.60, 147.37, 152.05, 153.77, 155.47; MS m/z 405 (M^+) Anal. ($C_{23}H_{27}N_5O_2$) C, H, N.

3-[(4-Phenylpiperazin-1-yl)methyl]-2,3-dihydroimidazo[1,2-c]quinazolin-5(6*H*)-one (27a). To a mixture of **26a** (0.34 g, 0.87 mmol) in methanol (30 mL) was added sodium hydroxide (5 g, 0.1 mol). The mixture was refluxed using an oil bath for 6 h. The mixture was then evaporated in vacuo to dryness. To the residue was added water (50 mL), and then the mixture was neutralized with acetic acid to pH 7. The resulting solid was collected by filtration to afford **27a** (0.29 g, 93%). An analytical sample was recrystallized from ethanol: mp 252–253 °C; UV λ_{max} nm ($\epsilon \times 10^4$): (methanol) 250 (1.8), 315 (0.5); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.45–2.80 (m, 6H, 3 CH_2), 3.08 (m, 4H, 2 CH_2), 3.86-4.06 (m, 2H, CH_2), 4.48 (m, 1H, CH), 6.73 (t, J = 7.3 Hz, 1H, Ar-H), 6.89 (d, J = 8.3 Hz, 2H, Ar-H), 7.06 (t, J = 9.3 Hz, 2H, Ar-H), 7.18 (t, J = 7.8 Hz, 2H, Ar-H), 7.47 (t, J = 7.8 Hz, 1H, Ar-H), 7.78 (d, J = 7.8 Hz, 1H, Ar-H), 10.55 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 48.10, 53.13, 53.71, 58.34, 59.03, 111.48, 114.92, 115.16, 118.54, 121.96, 125.47, 128.67, 132.79, 139.63, 148.00, 150.86, 152.41; MS m/z 361 (M^+), 296 (M^+ - 65), 285 (M^+ - 76), 275 (M^+ - 86), 175 (M^+ - 185, 100). Anal. ($C_{21}H_{23}N_5O$) C, H, N.

3-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-c]quinazolin-5(6*H*)-one (27b) was obtained in 34% yield using a procedure similar to that of **27a**. An anlytical sample was recrystallized from ethanol: mp 211–212 °C; IR (KBr) 1635, 1688, 2829, 2946, 3226 cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^4$) (methanol) 245 (0.7), 243 (0.7); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.45-2.85 (m, 6H, 3 CH_2), 2.95 (m, 4H, 2 CH_2), 3.77 (s, 3H, OCH_3), 3.87–4.08 (m, 2H, CH_2), 4.48 (m, 1H, CH), 6.86–6.94 (m, 4H, Ar-H),

7.09 (t, J = 6.5 Hz, 2H, Ar-H), 7.48 (t, J = 7.3 Hz, 1H, Ar-H), 7.80 (d, J = 8.3 Hz, 1H, Ar-H), 10.50 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 50.05, 53.60, 53.67, 55.25, 58.47, 59.34, 111.56, 111.85, 115.10, 117.85, 120.81, 122.13, 122.31, 125.58, 132.99, 139.79, 141.18, 148.13, 151.94, 152.54; MS m/z 391 (M^+), 376 (M^+ - 15), 205 (M^+ - 187, 100). Anal. ($C_{22}H_{25}N_5O_2$) C, H, N.

3-[[4-(2-Chlorophenyl)piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one (27c) was obtained in 68% yield using a procedure similar to that of **27a**. An anlytical sample was recrystallized from ethanol: mp 227–228 °C; UV λ_{max} nm ($\epsilon \times 10^4$) (methanol) 249 (1.4), 315 (0.6); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.45–2.86 (m, 6H, 3 CH_2), 2.94 (m, 4H, 2 CH_2), 3.85–4.06 (m, 2H, CH_2), 4.44–4.49 (m, 1H, CH), 6.98–7.12 (m, 4H, Ar-H), 7.25 (t, J = 7.8 Hz, 1H, Ar-H), 7.34 (d, J = 7.8 Hz, 1H, Ar-H), 7.45 (t, J = 7.4 Hz, 1H, Ar-H), 7.77 (d, J = 7.4 Hz, 1H, Ar-H), 10.51 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 50.82, 53.44, 53.67, 58.47, 59.23, 111.56, 115.05, 120.75, 122.13, 123.75, 125.58, 127.58, 127.98, 130.26, 132.97, 139.74, 148.09, 148.94, 152.50; MS m/z 395 (M^+). Anal. ($C_{21}H_{22}N_5ClO$) C, H, N.

3-[[4-(3-Methoxyphenyl)piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one (27d) was obtained in 90% yield using a procedure similar to that of **27a**. An anlytical sample was recrystallized from ethanol: mp 200–201 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47–2.93 (m, 6H, 3 CH_2), 3.09–4.12 (m, 4H, 2 CH_2), 3.70 (s, 3H, OCH_3), 4.00–4.14 (m, 2H, CH_2), 4.50–4.52 (m, 1H, CH), 6.32–6.45 (m, 3H, Ar-H), 6.92 (d, J = 8.3 Hz, 1H, Ar-H), 7.02-7.10 (m, 2H, Ar-H), 7.37 (t, J = 7.4 Hz, 1H, Ar-H), 7.87 (d, J = 7.8 Hz, 1H, Ar-H), 9.93 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.15, 53.23, 53.69, 54.81, 58.45, 59.16, 101.41, 104.06, 107.97, 111.56, 115.14, 122.11, 125.56, 129.53, 132.97, 139.83, 148.17, 152.34, 152.56, 160.15, 174.63; MS m/z 391 (M^+), 376 (M^+ - 15), 205 (M^+ - 186, 100). Anal. ($C_{22}H_{25}N_5O_2$) C, H, N.

3-[[4-(4-Methoxyphenyl)piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one (27e) was obtained in 99% yield using a procedure similar to that of **27a**. An anlytical sample was recrystallized from DMF: mp 250–251 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.50–2.82 (m, 6H, 3 CH_2), 2.98 (br s, 4H, 2 CH_2), 3.67 (s, 3H, OCH_3), 3.87–4.06 (m, 2H, CH_2), 4.47 (m, 1H, CH), 6.86 (d, J = 8.7 Hz, 2H, Ar-H), 6.79 (d, J = 8.7 Hz, 2H, Ar-H), 7.07 (d, J = 6.4 Hz, 2H, Ar-H), 7.45 (t, J = 7.3 Hz, 1H, Ar-H),, 7.78 (d, J = 7.8 Hz, 1H, Ar-H), 10.85 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.50, 53.27, 53.75, 55.08, 58.32, 59.03, 111.48, 114.17, 115.01, 117.15, 121.92, 125.44, 132.79, 139.76, 145.30, 148.06, 152.47, 152.78; MS m/z 391 (M^+), 376 (M^+ - 15), 205 (M^+ - 171, 100). Anal. ($C_{22}H_{25}N_5O_2$) C, H, N.

3-[(4-Phenylpiperazin-1-yl)methyl]-6-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one (28a) was prepared in 92% yield by a similar approach which afforde **20a**. An analytical sample was recrystallized from acetonitrile: mp 173–174 °C; UV λ_{max} nm ($\epsilon \times 10^4$) (methanol) 249 (1.0), 317 (0.4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50–2.82 (m, 6H, 3 CH_2), 2.95–3.00 (m, 1H, CH), 3.17 (m, 4H, 2 CH_2), 3.46 (s, 3H, CH_3), 4.04–4.17 (m, 1H, CH), 4.61 (m, 1H, CH), 6.84 (t, 1H, J = 7.32 Hz, Ar-H), 6.92 (d, 2H, J = 8.73 Hz, Ar-H), 7.07 (d, 1H, J = 8.43 Hz, Ar-H), 7.17 (t, 1H, J = 7.44 Hz, Ar-H), 7.25 (t, 2H, J = 8.43 Hz, Ar-H), 7.55 (t, 1H, J = 7.1 Hz, Ar-H), 8.04 (d, 1H, J = 7.74 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.23, 49.69, 54.37, 55.98, 59.64, 60.37, 113.83, 114.5, 116.57, 120.19, 123.37, 127.19, 129.63, 133.91, 141.31, 149.43, 151.88, 153.40; MS m/z 375. Anal. ($C_{22}H_{23}N_5O$) C, H, N.

3-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-6-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one (28b) was obtained in 65% yield using a procedure similar to that of **28a**. An analytical sample was prepared by recrystallization from CH_3CN: mp 147–148 °C; UV λ_{max} nm ($\epsilon \times 10^4$) (methanol) 249 (1.3), 279 (0.4); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.43–2.50 (m, 4H, 2 CH_2), 2.65 (m, 2H, CH_2), 2.80–2.94 (m, 4H, 2 CH_2), 3.36 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 3.85–4.07 (m, 2H, CH_2), 4.50 (m, 1H, CH), 6.85–6.93 (m, 4H, Ar-H), 7.17 (t, J = 7.8 Hz, 1H, Ar-H), 7.25 (d, J = 8.3 Hz, 1H, Ar-H), 7.59 (t, J = 7.4 Hz, 1H, Ar-H), 7.88 (d, J = 7.8 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 29.33, 50.02, 53.56, 54.79, 55.23, 58.30, 59.31, 11.85, 112.65, 114.57, 117.81, 120.77, 122.27, 125.71, 133.24, 140.43, 141.16, 148.06, 151.55, 151.92; MS m/z 405 (M+). Anal. ($C_{23}H_{27}N_5O_2$) C, H, N.

3-[[4-(2-Chlorophenyl)piperazin-1-yl]methyl]-6-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one (28c) was obtained in 90% yield using a procedure similar to that of **28a**. An analytical sample was recrystallized from ethanol: mp 154–155 °C; UV λ_{max} nm ($\epsilon \times 10^4$) (methanol) 252 (1.0), 317 (0.5); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.46–2.86 (m, 4H, 2 CH_2), 2.70 (br s, 1H, CH), 2.83–2.85 (m, 1H, CH), 2.96 (br s, 4H, 2 CH_2), 3.36 (s, 3H, CH_3), 3.86–3.91 (m, 1H, CH), 4.01–4.08 (m, 1H, CH), 4.52 (m, 1H, CH), 7.02 (t, J = 7.4 Hz, 1H, Ar-H), 7.13 (d, J = 8.3 Hz, 1H, Ar-H), 7.18 (t, J = 7.8 Hz, 1H, Ar-H), 7.28 (m, 2H, Ar-H), 7.38 (d, J = 7.8 Hz, 1H, Ar-H), 7.60 (t, J = 7.8 Hz, 1H, Ar-H), 7.89 (d, J = 7.8 Hz, 1H, Ar-H); ^{13}C NMR (100.40 MHz, DMSO-d_6) δ 29.37, 50.80, 53.42, 54.79, 58.28, 59.20, 112.65, 114.63, 120.77, 122.40, 123.75, 125.73, 127.54, 128.00, 130.25, 133.30, 140.47, 148.09, 148.94, 151.57; MS m/z 409 (M^+), 394 (M^+ - 15), 269 (M^+ - 140), 209 (M^+ - 200). Anal. ($C_{22}H_{24}N_5ClO$) C, H, N.

3-[[4-(3-Methoxyphenyl)piperazin-1-yl]methyl]-6-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one (28d) was obtained in 84% yield using a procedure similar to that of **28a**. An analytical sample was prepared by recrystallization from CH_3CN: mp 139–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50–2.98 (m, 6H, 3 CH_2), 3.16–3.17 (m, 4H, 2 CH_2), 3.45 (s, 3H, OCH_3), 3.77 (s, 3H, CH_3), 4.05–4.18 (m, 2H, CH_2), 4.59 (m, 1H, CH), 6.40 (d, J = 8.3 Hz, 1H, Ar-H), 6.44 (s, 1H, Ar-H), 6.51 (d, J = 8.3 Hz, 1H, Ar-H), 7.06 (d, J = 8.3 Hz, 1H, Ar-H), 7.13–7.26 (m, 3H, Ar-H), 7.54 (t, J = 8.3 Hz, 1H, Ar-H), 8.03 (d, J = 7.8 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.91, 49.28, 53.99, 55.40, 55.64, 59.28, 60.05, 102.64, 104.65, 109.04, 113.47, 114.20, 123.07, 126.87, 129.98, 133.62, 140.99, 149.09, 152.93, 153.10, 160.80; MS m/z 405 (M^+). Anal. ($C_{23}H_{27}N_5O_2$) C, H, N.

Antihypertensive Activity. Spotaneously hypertensive rats of either sex, 250–300 g, anesthetized with pentobarbital sodium (40–50 mg/kg ip) were used. Both femoral artery and vein were cannulated with PE 150 tubing to monitor blood pressure and for drug administration, respectively. Body temperature was maintained at 37.5 °C with a heating pad and monitored with a rectal thermometer. Blood pressure was measured with a Statham P23D pressure transducer via a polyethylene cannula placed in the right femoral artery. Heart rate was measured through a Grass Model 7B tachograph preamplifier triggered by the pulses of arterial blood pressure. All data were recorded on a Grass Model 7B polygraph.

Methods of Binding Studies. 1. Preparation of Membranes for Binding Studies. Rat brain cortex membranes are prepared for [^{3}H]prazosin or [^{3}H]clonidine binding by homogenizing tissues 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 1000g for 10 min, P_2 membranes were pelleted by centrifuging the supernatant at 22000g for 20 min. After two periods of centrifugation at 22000g and resuspension in fresh buffer, the membrane suspension (about 2 mg/mL protein) is ready for use.

2. Binding Assays. α_1-Adrenergic receptor binding assays (in triplicate) were carried out with either 0.01–1 nM [^{3}H]prazosin for saturation binding studies or 0.2 nM [^{3}H]prazocin for competition binding studies 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 are in the range of 0.1–200 nM.

α_2-Adrenergic receptor binding assays (in triplicate) were carried out with either 0.1–10 nM [^{3}H]clonidine for saturation binding studies or 1 nM [^{3}H]clonidine for competition binding studies in the presence of 10 mM $MgCl_2$ 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 clonidine to determine nonspecific binding. The concentrations of each compound for competition binding are 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.[21]

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