= 0.99 ● 0.03) with a K_D of 1.34 ● 0.12 nM and a B_{max} of 45.8 ± 3.0 fmol/mg of protein. Data were analyzed by using the computer programs EBDA and LIGAND, described elsewhere.[25] Protein concentrations were determined according to the method of Bradford.[26] Values for free energy of binding at 37 °C (310 K) were calculated from $\Delta G^0 = -RT \ln K_A$.[19]

Acknowledgment. Support for this work was provided by USPHS Grant DA-02189 from the National Institute on Drug Abuse. We also thank Jim Schirger for assistance with the early synthetic work.

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Synthesis and Benzodiazepine Binding Activity of a Series of Novel [1,2,4]Triazolo[1,5-*c*]quinazolin-5(6*H*)-ones

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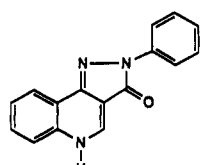
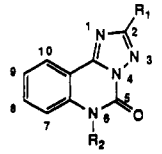
Investigation of tricyclic heterocycles related to the 2-arylpyrazolo[4,3-*c*]quinolin-3(5*H*)-ones, structures with high affinity for the benzodiazepine (BZ) receptor, led to the synthesis of 2-phenyl-[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one, a compound with 4 nM binding affinity to the BZ receptor. Analogues were prepared to assess the importance of the 2-substituent and ring substitution in modifying activity. Several novel synthetic routes were designed to prepare the target compounds, including a two-step synthesis beginning with an anthranilonitrile and a hydrazide. Of the 34 compounds screened in this series, three compounds were found to be potent BZ antagonists in rat models. The leading compound, 9-chloro-2-(2-fluorophenyl)[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one (CGS 16228), showed activity comparable to that of CGS 8216 from the pyrazolo[4,3-*c*]quinoline series.

The discovery of CGS 8216 (1) at CIBA-GEIGY as a potent benzodiazepine (BZ) receptor antagonist[1] pioneered our efforts in the investigation of other tricyclic heterocycles of similar molecular size and shape. In 1972, CGS 1761 (**2a**)[2] and CGS 1792 (**2b**) were screened for overt effects in the rat and were thought to have weak anxiolytic profiles.[3] Although these compounds were found later to have poor binding to the BZ receptor (i.e., with an IC_{50} value greater than 1 μM), replacement of the trifluoromethyl group of **2a** by the phenyl moiety produced a structure that mimicked the size and shape of 1 very closely, except for the position of the carbonyl group. This compound, CGS 13767 (**2c**), showed a BZ binding affinity IC_{50} value of 4 nM, a substantial improvement over the values for **2a** and **2b**, though not quite as impressive as that for 1.[1] Modifications of **2c** were designed to assess the importance of the 2-substituent, the oxo group, and selected substitution in the benzene ring.



1: CGS 8216

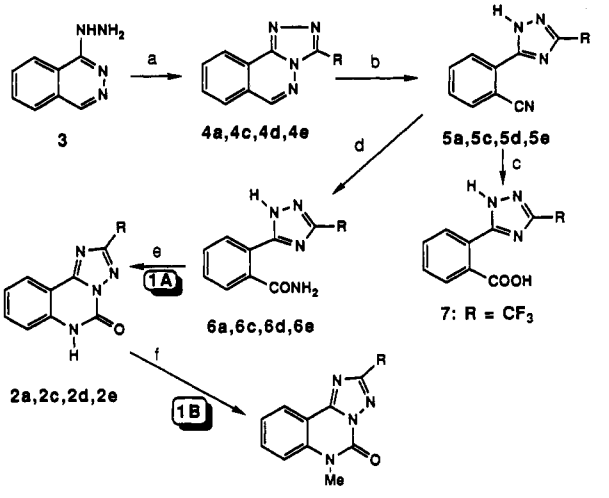


2a: R_1 = CF_3 R_2 = H

2b: R_1 = CF_3 R_2 = CH_3

2c: R_1 = Phenyl R_2 = H

Scheme I. Methods 1A and 1B[a]



a: R = CF_3 c: R = phenyl d: R = 4-chlorophenyl e: R = 3-pyridyl

[a] Reagents: (a) RCOOH, RCOOCOR, or RCOCl, NaOH, THF or (i) RCHO, MeOH, (ii) Br_2, HOAc, Ac_2O; (b) NaOH, EtOH, or NaOMe, EtOH; (c) (i) 10 N NaOH, (ii) HCl; (d) 85% H_2SO_4; (e) NaBrO, H_2O or $Pb(OAc)_4$, DMF with Et_3N or HOAc; (f) NaH or NaOMe, DMSO, MeI.

Chemistry

A Sandoz patent[4] described the synthesis of 8,9-dimethoxy[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one by hydrolysis and Dimroth rearrangement[5] of 5-chloro-8,9-di-

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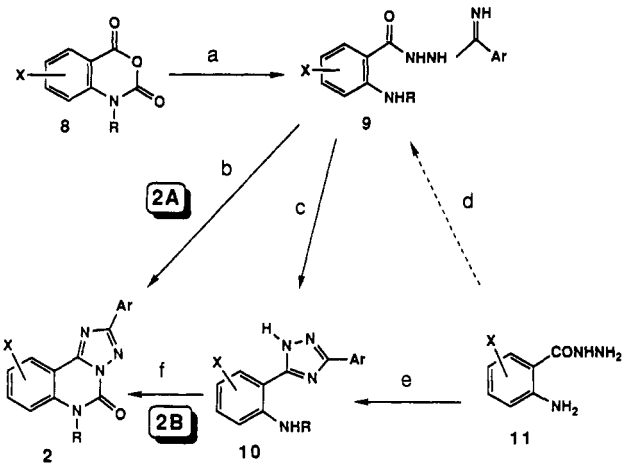
0022-2623/91/1834-0281$02.50/0

Scheme II. Methods 2A and 2B[a]

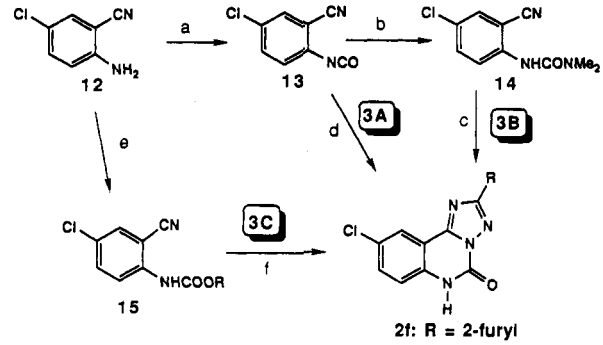


[a] Reagents: (a) $ArC(=NH)NHNH_2$, pyridine; (b) $H_2NCOOC_2H_5$; (c) PhOPh, tri-*n*-propylamine or PhOPh, PhPh; (d) $ArC(=NH)OEt$; (e) $ArC(=NH)NH_2$, NaOMe, EtOH; (f) $H_2NCOOEt$ or $ClCOOCCl_3$.

methoxy[1,2,4]triazolo[4,3-*c*]quinazoline. A modified Curtius rearrangement[6] of the azide of *o*-[5-(trifluoromethyl)-*s*-triazol-3-yl)benzoic acid[7] (**7**, Scheme I) led to the first published synthesis of **2a**.[2] During our work, a patent appeared describing the synthesis of [1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-ones substituted at the 2-position by a carboxyl, ester, amide, cyano, or tetrazolyl group, with examples of substitution in the 6-, 7-, 9-, and 10-positions.[8] In this patent, the ring system was prepared by the known method[4] and by reaction of a 3-(*o*-aminophenyl)-1,2,4-triazole with phosgene or a phosgene equivalent (vide infra).

We discovered a synthetic route to 2-aryl[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-ones during the investigation of the Hofmann degradation of amide **6** (Scheme I), prepared in three steps from 1-hydrazinophthalazine[9] (**3**) by the reaction sequence shown in method 1A of Scheme I. Ring cleavage of **4** to **5** was a key step in the procedure.[10] Conversion of the nitrile **5a** to the amide **6a** was achieved cleanly with sulfuric acid, whereas strong alkali led to acid **7**, previously prepared by another route.[7] Treatment of the amide with sodium hypobromite followed by acidification led to **2a**. Since **2a** remained unchanged after treatment with refluxing trifluoroacetic acid, the [1,2,4]-triazolo[1,5-*c*]quinazolin-5(6*H*)-one structure is favored over the [4,3-*c*] isomer.[4] The amide is converted to the corresponding isocyanate,[2] which cyclizes during the reaction. Examples in which the 2-substituent is hydrogen, 4-chlorophenyl (**2d**), or 3-pyridyl (**2e**) were attempted by this procedure, but the end products contained impurities that were difficult to remove. The 2-phenyl analogue **2c**, as well as **2d** and **2e**, were prepared cleanly by treatment of the amide with lead tetraacetate in dimethylformamide instead of using hypohalite. In the sequence to prepare **2e**, the *s*-triazolo[3,4-*a*]phthalazine **4e** was prepared by reaction of **3** with nicotinaldehyde followed by bromination in acetic acid containing sodium acetate.[11] The 3-phenyl

Scheme III. Methods 3A, 3B, and 3C[a]



[a] Reagents: (a) $Cl_3COCOCl$, dioxane; (b) Me_2NH, toluene; (c) 2-furoylhydrazine, $MeOCH_2CH_2OH$; (d) 2-furoylhydrazine, tri-*n*-propylamine, $MeOCH_2CH_2OH$; (e) MeOCOCl or EtOCOCl, Na_2CO_3, MeCOEt; (f) 2-furoylhydrazine, tri-*n*-propylamine, $MeOCH_2CH_2OH$.

analogue **4c**[9] was prepared in the same manner. Reaction of **3** with an acid chloride or anhydride followed by either spontaneous cyclization or heat treatment is the usual method.[12] The 6-position of the heterocycle was methylated by forming the anion with sodium hydride or sodium methoxide in dimethyl sulfoxide or dimethylformamide at 60 °C followed by treatment of the cooled mixture with methyl iodide (method 1B in Scheme I).

A second method of forming the desired ring system (method 2A in Scheme II) required the preparation of an *o*-aminobenzoylamidrazone[13] (**9**). Analogues substituted at the 2-position by pyridine were prepared by reaction of an isatoic anhydride (**8**) under basic conditions with a pyridylamidrazone.[13] These amidrazones were readily prepared from the cyanopyridine and hydrazine.[14] On heating in an excess of ethyl carbamate, the acylamidrazone was first cyclized to the 3-(*o*-aminophenyl)-5-substituted-1,2,4-triazole (**10**). This reacted further with the excess carbamate to introduce the carbonyl group into the tricyclic heterocycle through a urethane, isocyanate, or urea intermediate. Alternatively, the preformed triazole, obtained by heating the acylamidrazone at high temperature (diphenyl ether, tri-*n*-propylamine, 200 °C, 2 h) was reacted with ethyl carbamate or trichloromethyl chloroformate,[8] to form the target compound (method 2B in Scheme II).[15] Reaction of the hydrazide of an anthranilic acid (**11**) with an imidic ester followed by fusion of the isolated acylamidrazone is the known method for producing 3,5-disubstituted 1,2,4-triazoles[16] (**11** to **9** to **10**). This was replaced by a more convenient method, i.e., the reaction of **11** with an amidine.[17] Attempts to react an

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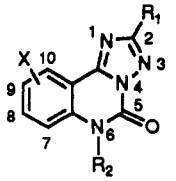
Table I. Diazepam Binding Data



no.	R_1	R_2	X	method (yield, %)[a]	mp, °C	DZ binding: IC_{50}, nM
2a	CF_3	H	H	1 (50)	288–293	>1000
2b	CF_3	CH_3	H	1B (56)	226–229	>1000
2c	Ph	H	H	1 (56)	311–313	4
2d	4-ClC_6H_4	H	H	1 (72)	315–318	>10000
2e	3-pyridyl	H	H	1 (32)	268–271[b]	130
2h	4-pyridyl	H	H	2A (51)	271–273[b]	200
2i	2-pyridyl	H	9-Cl	2B (88)	>340	100
2j	Ph	H	7,9-Cl_2	2B (62)	309–311	200
2k	Ph	CH_3	H	1B (96)	231–234	350
2l	3-pyridyl	H	9-Cl	2A (21)	320–322[b]	10
2m	3-pyridyl	CH_3	H	1B (36)	217–219[b]	>10000
diazepam						4.0[c]
flunitrazepam						1.5[d]
1 (CGS 8216)						0.3[d]

[a] Purified yield. [b] *p*-Toluenesulfonate salt. [c] 4.04 ± 0.10 (n = 36). [d] Reference 1b.

imidic ester hydrochloride with **11** in the presence of triethylamine led to a 1,3,4-oxadiazole (see the Experimental Section).

A much shorter method (method 3A, Scheme III) for preparing the target compounds, disclosed in an earlier publication,[15] involved the conversion of an anthranilonitrile, e.g. 5-chloroanthranilonitrile (**12**), to its *o*-cyano isocyanate **13** with trichloromethyl chloroformate followed by treatment with a hydrazide to form the desired targets in two steps. Initially we chose ring-closure conditions of an inert solvent (dioxane) at 80 °C over several hours followed by ammonia in ethanol because of a similar base-catalyzed condensation described by Papadopoulus.[18] Since the isocyanate was sensitive to moisture, we looked for more stable intermediates. Treatment of the isocyanate with dimethylamine at room temperature gave the stable urea **14**, which reacted with 2-furoic acid hydrazide in refluxing 2-methoxyethanol within 1 h to give the desired product **2f** (method 3B, Scheme III).

The preferred method (3C, Scheme III) does not require phosgene or its equivalent and makes use of a stable intermediate. Reaction of **12** with methyl or ethyl chloroformate in 2-butanone in the presence of sodium bicarbonate gave a stable urethane **15**. This was reacted with a hydrazide to form the desired tricyclic target, as illustrated for **2f**. Conditions chosen were reflux in a mixture of 2-methoxyethanol and tri-*n*-propylamine. Subsequently it was discovered that heating the urethane and hydrazide in 1-methyl-2-pyrrolidinone alone produced the end product in good yield.[19] This method was further improved[19] by refluxing the anthranilonitrile in ethyl chloroformate, from which the ethylurethane and unreacted solvent could be recovered.

The strong carbonyl absorption in the 1730–1760-cm^{-1} region of the infrared spectrum is indicative of the amide rather than the imidic acid tautomer for the [1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-ones. Alkylation of the unsubstituted amide under basic conditions gave compounds **2b**, **2k**, and **2m** with an equally prominent carbonyl absorption, indicating N-alkylation rather than O-alkylation. Furthermore, **2k** showed a strong NOE effect between the protons of the methyl group at N-6 (δ = 3.74 ppm) and the hydrogen at C-7 indicative of close spacial proximity. Also, the ^{13}C spectral analysis showed that the methyl protons are scalar-coupled to both C-5 and C-6a via three-bond interactions. Selective decoupling at 3.74 ppm caused the C-5 signal to collapse from a quartet (J = 3.2 Hz) to a singlet and caused a substantial sharpening of the broad C-6a carbon to a discernible triplet of doublets, due to two three-bond couplings to H-8 and H-10 and one two-bond coupling to H-7. These results are not explicable for an O-methylated compound. To define the importance of the carbonyl group for receptor binding, we prepared and screened examples of 2-phenyl[1,2,4]triazolo[1,5-*c*]quinazolines with hydrogen (**16**), methyl (**17**), phenyl (**18**),[20] chloro (**19**), and amino (**20**) at the 5-position as described in the Experimental Section.

Biological Test Results

Relative activities of the analogues of **2c** shown in Table I were assessed by testing each compound for displacement of [^{3}H]diazepam from rat forebrain BZ receptors.[21,22] Later, analogues were screened for displacement of [^{3}H]-flunitrazepam (FNZ), a better ligand,[1b] from rat forebrain BZ receptors[23] (Table II). Since IC_{50} values were not markedly different from one ligand to the other for standard compounds,[1] we assumed that our decision to select compounds on the basis of IC_{50} comparisons would be unaffected by the procedural change. To assess the oral activity of the more promising analogues, in vivo displacement of FNZ from mouse whole brain was carried out by a modified procedure of Chang and Snyder.[24] (See the Experimental Section).

Table I shows that the binding affinity of **2c** is comparable to that of diazepam but that **2c** is 10-fold less potent than **1**. Surprisingly, the binding affinity of **2d** was very poor, but its insolubility in the test medium is thought to

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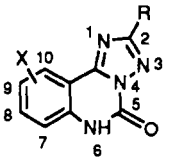
(24) Chang, R. S. L.; Snyder, S. H. *Eur. J. Pharmacol.* **1978**, *48*, 213.

Table II. Flunitrazepam Binding Data



no.	R	X	method (yield, %)[a]	mp, °C	FNZ binding: IC_{50},[b] nM
2f	2-furanyl	9-Cl	3A (33)	>340	0.6
			2B (36)	375–377	
			3B (88)	>340	
			3C (65)	>340	
2g	Ph	9-Cl	2B (71)	>340	8
2n	3-furanyl	9-Cl	2B (54)	>350	3.5
2o	2-thienyl	9-Cl	2B (33)	>330	0.6
2p	$2\text{-FC}_6\text{H}_4$	H	3A (39)	326–329	0.4
2q	benzyl	9-Cl	3A (13)	282–284	100
2r	$2\text{-FC}_6\text{H}_4$	9-Cl	2B (87)	>350	0.4
			3A (92)	>350	
2s	$3\text{-FC}_6\text{H}_4$	9-Cl	2B (54)	>320	4
2t	$4\text{-FC}_6\text{H}_4$	9-Cl	2B (58)	>320	20
2u	*p*-tolyl	9-Cl	2B (70)	>320	200
2v	$4\text{-MeOC}_6\text{H}_4$	9-Cl	2B (71)	>320	3
2w	$4\text{-HOC}_6\text{H}_4$	9-Cl	3A (18)	>350	0.3
2x	$4\text{-CF}_3\text{C}_6\text{H}_4$	9-Cl	2B (80)	334–336	>1000
2y	$3,4,5\text{-MeOC}_6\text{H}_4$	9-Cl	2B (61)	>290	>1000
2z	3-(*N*-methylpiperidyl)	9-Cl	3A (5)	274–276[c]	>1000
2aa	tetrahydro-2-furanyl	9-Cl	3A (34)	241–243	>100
2bb	hydroxymethyl	H	3A (49)	295–300	>100
2cc	carbethoxy	H	3A (12)	288–291	2.5

[a] Last step yield. [b] DZ: IC_{50} = 4.4 ± 0.2 (n = 13). [c] Fumarate.

be the cause of this unexpected result. Replacement of phenyl at the 2-position by pyridyl (**2e**, **2h**) allowed the formulation of soluble salts, but affinity to the receptor was diminished. Introduction of chlorine at the 9-position as in **21** vs **2e** increased binding affinity. Introduction of methyl at the 6-position (**2k**, **2m**) diminished affinity markedly. The introduction of two substituents in the benzene ring (**2j**) was unpromising. Compounds in which there was no 5-carbonyl group (**16–20**) demonstrated *no significant diazepam binding affinity* (i.e., less than 50% displacement of diazepam at 1 μM, data not shown).

Table II shows the comparative binding affinity of selected analogues in the FNZ binding assay. High affinity was maintained when the phenyl at position 2 was replaced by the heteroaryl groups furan and thiophene, whether 2- or 3-annelated (**2f** vs **2n**). Non-heteroaromatic substituents (**2z**, **2aa**) or aralkyl moieties (**2q**) produced compounds with poor binding affinity values. Substitution of hydrogen in the appended phenyl of **2g** by fluorine, *p*-methoxy, or *p*-hydroxy gave compounds with good binding affinity values. The *o*-fluorophenyl derivatives (**2p**, **2r**) were superior to the meta and para isomers (**2s**, **2t**). The 2-carbethoxy derivative **2cc** was also very potent in binding to the receptor.

Further differentiation of the compounds was observed during in vivo FNZ binding, a test that we used as an indicator of oral activity and a criterion for further evaluation. Table III shows that **2w** and **2cc**, despite excellent binding affinity, displayed no activity in vivo at 30 mg/kg. Five other compounds were disappointing in terms of their oral potency (**2f**, **2h**, **2j**, **21**, **2o**). As expected from the binding results, those with a methylene group at the 2-position (**2q**, **2bb**) were not only poor in binding affinity but also inactive orally. The remaining compounds were considered worthy of further investigation.

Table III. Comparison of Binding Data in Vitro with FNZ Binding in Vivo

no.	BZ binding: IC_{50}, nM	FNZ binding: IC_{50}, nM	FNZ in vivo, po: % inhibn at 30 mg/kg
2c	4		55
2e	130		48
2f		0.6	15
2g		8	72
2h	200		19
2j	200		6
2k	350		55
2l	10		24
2o		0.6	21
2p		0.4	41
2q		100	0
2r		0.4	76[a]
2s		4	31
2t		20	52
2u		200	63
2w		0.3	0
2bb		>100/<1000	0
2cc		2.5	0
1	0.3	4.4	90

[a] n = 2.

All of our [1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-ones were tested orally in rats at 30 mg/kg for effects on rotorod performance and ability to protect against Metrazole (pentylenetetrazole) induced seizures (part of NRPS screening, as described in the Experimental Section). Since none of the compounds showed activity (data not shown), there was no reason to expect BZ agonist activity in this series. Therefore, our lead compounds were compared with **1**.

In the next stage of screening, drugs were tested for their ability to antagonize the action of diazepam in overcoming the convulsive effects of Metrazole. Predosing of rats with 7.5 mg/kg of diazepam orally blocks the convulsant effect of 30 mg/kg iv of Metrazole administered 1 h later, but this effect is negated by a BZ antagonist. In support of the FNZ in vivo results, **2h**, **2l**, and **2j** were inactive at 30 mg/kg ip whereas **2e** and **2k** showed an ED_{50} value of 30 mg/kg ip in antagonizing the effect of diazepam. Compound **2u**, promising in the FNZ in vivo test, was inactive at 30 mg/kg and **2o** appeared more active than expected with an ED_{50} value of at least 10 mg/kg. Compound **2c** appeared effective in 50% of the animals at 10 mg/kg and **2t** was active at 10 mg/kg i.p. These nine compounds were not further pursued because **1** was active at 3 mg/kg in this test.

Since **2r** appeared more effective orally than the closely related structure **2p**, the three compounds **2r**, **2g**, and **2s** were studied further (Table IV). All had ED_{50} values of 1 mg/kg or less in the Metrazole test. They were then tested for their ability to antagonize diazepam-induced rotorod deficit. In one protocol, the test compound was administered ip at different doses and challenged 3 h later with 30 mg/kg po of diazepam. The rotorod challenge was given 1 h later. Under these conditions, **2r** and **2g** had ED_{50} values of 7 and 26 mg/kg, respectively. Compound **2s**, ineffective at 30 mg/kg, was not further investigated. When rats were given various doses of drug orally followed 30 min later by 30 mg/kg ip of diazepam and then challenged 30 min thereafter on the rotorod, **2g** appeared more potent than **2r**, with ED_{50} values of 2.8 and 5.5 mg/kg, respectively. Compound **2r** (CGS 16228) was then tested for its ability to antagonize diazepam-induced discriminative stimuli in rats.[25] Against a dose of 10 mg/kg po

(25) Bennett, D. A.; Amrick, C. L.; Wilson, D. E.; Bernard, P. S.; Yokoyama, N.; Liebman, J. M. *Drug Dev. Res.* **1985**, *6*, 3134.

Table IV. Comparison of Selected Benzodiazepine Antagonists

agent	FNZ binding: IC_{50}	antag of DZ-induced rotorod deficit: ED_{50}, mg/kg	antag of DZ effect vs metrazole: dose (ip)	antag of DZ effect vs metrazole: no. of animals protected	drug discrimination antagonism of diazepam: ED_{50}, mg/kg
2r	0.4	6.92 (5.72–8.38)* [b] ip	30	0/6	2.99 (1.34–8.6)* ip
			10	0/6	
		5.5 (2.5–12.7)* po	3	2/6	6.51 (2.16–24.1)* po
			1	2/6	
			0.3	6/6	
2s	4.0	>30 ip	30	0/6	not run
			10	0/6	
			3	2/6	
			1	1/6	
			0.3	5/6	
2g	8.0	26 (21.6–30.6)* ip	30	0/6	not run
			10	0/6	
		2.8 (0.6–9.6)* po	3	2/6	
			1	3/6	
			0.3	6/6	
1 [a]	0.3	0.6 (0.3–1.2)* po	20	0/6	1.61 (0.85–2.9)* po
			10	0/6	
			3	1/6	
			1	5/6	

[a] References 1b, 25, 31. [b] 95% confidence limits.

of diazepam, ED_{50} values for **2r** were 3 mg/kg ip and 6.5 mg/kg po. As shown by comparison in Table IV, **2r** was somewhat less active than **1** in two of the three tests but slightly more effective in the Metrazole screen.

During the course of our studies, the concept emerged of the BZ receptor as a complex involving γ-aminobutyric acid (GABA) and a chloride channel.[26] By the use of a procedure for [^{3}H]FNZ binding in which membranes were well washed to remove GABA, it was shown that GABA, when added, increases the affinity of BZ agonists for their receptor sites[27] whereas GABA reduces the affinity with some inverse agonists.[28] It was further postulated that true BZ antagonists would not affect the "GABA ratio".[28] In this procedure (see the Experimental Section), we found that **2r** showed an IC_{50} binding value of 0.5 nM and a GABA ratio of 0.79 compared to values of 0.37 nM and 0.82, respectively, for **1**.[29] These two compounds would fall into the "inverse agonist" category, as defined above.

Compound **1** was found to reduce the food intake in food-deprived rats[30] at doses of 3–100 mg/kg po. Under the same conditions, doses of 3–30 mg/kg po of **2r** had no significant effect on food consumption.

Discussion

The thrust of our research in the [1,2,4]triazolo[1,5-*c*]quinazolines was to find a potent, orally active anxiomodulator that could be readily prepared from commercially available starting materials. Our limited choice of analogues allowed certain general conclusions regarding the structure–activity relationship (SAR) in this series. The 5-carbonyl group is essential for BZ receptor binding. Alkylation at the 6-position significantly reduced binding affinity, indicating that the 6-proton plays a role in the binding. Benzene ring substitution was illustrated only by 9-chloro and 7,9-dichloro analogues and the single substituent is favored over disubstitution. The 2-substituent is very important for achieving receptor affinity in the low nanomolar or subnanomolar range. Our results show that a phenyl or a heteroaromatic substituent directly attached to the tricyclic system is essential for high affinity. Results from binding data on the pyridyl compounds suggest that a π-excessive heterocycle is a better choice than a π-deficient heterocyclic 2-substituent. An exception was the 2-carbethoxy group, which imparted good binding affinity but no oral activity. High affinity of substituted 2-phenyl analogues was maintained in compounds bearing a single halogen, hydroxyl, methoxyl, or methyl group but was lost with trifluoromethyl or trimethoxyl substitution, indicative of a size limitation in this area of the binding site.

The efficacy of **1** in overcoming the anticonvulsant, muscle relaxant, anxiolytic, and sedative properties of diazepam was demonstrated in four animal models.[31] The effects of **2r** in overcoming the efficacy of diazepam in blocking metrazole-induced convulsions and the efficacy of **2r** in blocking rotorod impairment induced by diazepam showed similarity with **1** in the first two criteria. Antagonism of diazepam-induced discriminative stimuli is another indication of BZ antagonist activity, and **2r** was very active both ip and po. However, **2r** has not been tested in the hexobarbital-induced-sleep–time procedure[31] or in the Cook–Davidson procedure[32] to assess the last two criteria. Further tests are needed to delineate the similarities and differences of this compound from other BZ antagonists and/or inverse agonists.

Examination of 2-phenyl-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3(5*H*)-ones led to compounds with antagonist and/or inverse agonist, agonist, or mixed agonist–antagonist properties.[1a] These marked differences in activity were caused merely by replacing the hydrogen in the para position of the appended phenyl by a chloro or methoxy

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(27) (a) Costa, T.; Rodbard, D.; Pert, C. B. *Nature* **1979**, *277*, 315. (b) Olsen, R. W. *J. Neurochem.* **1981**, *37*(1), 1 (Review).
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group.[1a] Replacement of the 2-aryl group with 2-methylthienyl unveiled a marked difference between the 2-methyl-4-thienyl isomer, an inverse agonist, and the 2-methyl-5-thienyl compound, an agonist.[33] Similarly, modification of the β-carboline structure has led to compounds with a full spectrum of biological activity at the BZ receptor complex[34] from anxiolytic to anxiogenic effects. Modification of the benzodiazepine structure through five-membered ring annelation[35] produced a BZ agonist, a partial agonist, and an inverse agonist. A series of 7,12-dihydropyrido[3,4-*b*:5,4-*b'*]diindoles also showed a range of activities with small changes in the substitution pattern.[36] Yet, only antagonists and/or inverse agonists were found among the 29 [1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-ones reported in this study. It could be argued that a different choice of substituents might have led to agonists and/or partial agonists. The new synthetic methods we have devised illustrate methodology for preparing other analogues from starting materials more readily accessible than those described in the earlier literature. This remains as a task for other interested investigators.

Several teams of scientists have proposed models to define the BZ receptor.[37] Of particular interest to us is the model of Codding and Muir,[37d] which was defined to explain the binding of antagonists as well as agonists. In our view, this model does not adequately explain the high affinity of our compounds. Structure **2r** would recognize three of the four features of the proposed binding site, but the carbonyl function of our molecule does not coincide with the position occupied by carbonyl in the proposed model. Since the carbonyl is vitally important for binding in our series, any proposed model should accommodate this feature.

A possible link between benzodiazepines and adenosine[38] led to the finding that **1** showed some adenosine antagonist activity in a functional assay[1b] whereas two other known antagonists and/or inverse agonists were essentially inactive. It is noteworthy that **2f** has high affinity for BZ receptors yet no significant affinity (10 μm or less) for adenosine receptors.[15] However, replacement of the 5-oxo group of **2f** by amino led to CGS 15943, a compound that showed high affinity for both A_1 and A_2 receptors[15] and no significant binding to BZ receptors.[39] On the basis of many in vitro and in vivo experiments, it has been proposed that inhibition of adenosine uptake accounts for many of the actions of BZs and that proconvulsant β-carbolines are adenosine antagonists.[38] Further studies utilizing **2r** may help to define the putative link between BZ receptors and adenosine.

As new biochemical, pharmacological, and now clinical information appears, the classification of BZ-receptor-active drugs into categories is continually being redefined.[40] The differentiation of antagonists and inverse agonists has important implications in choosing compounds for clinical trial. BZ antagonists or inverse agonists are potentially useful as agents for reversing the properties of diazepam in situations of overdose or postoperative treatment. Also, these drugs may have utility as cognitive enhancers[1b] and appetite suppressants.[30] However, some of these agents have shown anxiogenic[41] and proconvulsant[28b] effects in animal models and in clinical trials. Clearly there is a keen interest in finding definitive test procedures to predict more accurately desirable clinical effects and potentially dangerous side effects.[41a,42] The orally active test compound **2r** is a new chemical entity to aid the drug developer in this challenge.

The effect of replacement of the benzene ring of the [1,2,4]triazolo[1,5-*c*]quinazoline structure was also investigated,[43] and results will be published in due course.

Summary

In a study of 2-substituted [1,2,4]triazolo[1,5-*c*]-quinazolin-5(6*H*)-ones, one target (**2r**) was found with activity comparable to that of the BZ antagonist and/or inverse agonist **1** in vitro and in vivo. Novel synthetic routes were devised for this series of compounds. The simplest route yielded the lead compound in only two steps from commercially available chemicals. This novel structure is a new tool for research in the anxiomodulator field.

Experimental Section

Pharmacological Test Procedures. Neuropharmacology Rat Primary Screen (NRPS). Fasted male rats (140–170 g) were given the test compound at 30 mg/kg po. At the indicated time postdosing, the following tests were performed:

1. At 45 min postdosing:

A. Gross observations: animals were observed for signs of neurotoxicity, toxicity, or other effects prohibiting further testing.

B. Rotorod performance: rats were placed on a rotorod which was rotating at 16 rpm. A reactor was a rat unable to remain on the rotorod for 30 s within three trials.

C. Rat catalepsy: rats were placed on four rubber stoppers. A reactor was a rat remaining in place for 15 s within three trials.

2. At 90 min postdosing:

A. Rat Metrazole: Rats received 30 mg/kg Metrazole (12 mg/mL) iv and were observed for clonic seizure of >5 s duration within 60 s. A reactor showed no seizure.

B. Maximal electroshock: Rats received 150-mA shock at 0.2-s duration via corneal electrodes and were observed for tonic seizure. A reactor showed no seizure.

In Vitro [^{3}H]Diazepam Binding Screen. Compounds were tested for displacement of [^{3}H]DZ from rat cerebral cortex synaptosomal membranes as described by Braestrup and Squires[21] and by Moehler and Okada.[22] IC_{50} values were determined graphically on the basis of four to six drug concentrations. With

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each test group of compounds, diazepam was run as a control, IC_{50} = 4.04 ± 0.10 (n = 36).

In Vitro [^{3}H]Flunitrazepam Binding Screen. Compounds were evaluated for displacement of [^{3}H]FNZ from rat forebrain crude membranes homogenized and rinsed twice. Incubation time was 45 min at 0 °C. This ligand has higher affinity for the BZ receptors than DZ. The method is essentially that of Braestrup and Squires.[23] In this procedure, the geometrical mean of diazepam IC_{50}s was 4.4 ± 0.2 nM (n = 13).

In Vivo Interaction of Drugs with the Specific Binding of Tritiated Flunitrazepam in Mouse Whole Brain. Male Swiss mice (Mbf:SW) from Marland Breeding Farms, Hewitt, NJ (18–35 g, usually 16–18 g) were allowed free access to food and water and allowed to accommodate to the animal quarters for 1 week. Cornstarch suspension contained 3% cornstarch, 5% PEG-400, and 0.336% Tween 80. Test compounds were prepared fresh as 6 mg of base/mL of suspension, and if a dose–response curve was run, at least two dilutions (1:3 and 1:10) were used. Tritiated flunitrazepam ([^{3}H]FNZ) (NEN, >60 Ci/mmol) was diluted with normal saline (0.9%) such that 0.1 mL can be injected into the mouse for a final dose of 40 pmol/mouse. As the reference, clonazepam (6 mg/mL) was used. Mice were administered orally either cornstarch suspension, test compound, or clonazepam in a volume of 0.1 mL/20 g body weight. Thirty minutes later, 0.1 mL of diluted [^{3}H]FNZ was injected into the tail vein. Two minutes later, the mouse was sacrified by cervical dislocation and the brain removed and frozen in dry ice. It was weighed and then homogenized with a Brinkman Polytron (Model PCU-2-110, setting full speed, 30-s duration) in 30 volumes of cold "homogenization" buffer (Tris-HCl, 50 mM, pH 7.7). Triplicate 1-mL samples were filtered under vacuum through Whatman GF/B filters and the filters rinsed with 5-mL portions of cold "rinse" buffer (1:20 dilution of "homogenization" buffer with water). Filters were placed in miniscintillation vials with 5 mL of Scinti-Verse II, the vials were allowed to stand overnight, and radioactivity was determined in a liquid scintillation counter. Specific binding was defined as the difference in binding between groups of mice treated with test compounds and those treated with reference compound. The mean cpm (counts per minute) of the mice treated with clonazepam was subtracted from the mean cpm for each group of mice (dsb, drug specific binding). Control specific binding (csb) was the value obtained from the cornstarch treated mice. The percent inhibition was determined by the equation 100 × (csb) − (dsb)/(csb).

Antagonism of the Diazepam Anticonvulsant Effect against Metrazole. Fasted male rats weighing 120–180 g were given either the test compound, diazepam (7.5 mg/kg po), the test compound and diazepam (interaction group), or corn starch vehicle. Sixty minutes later, Metrazole (30 mg/kg iv) was administered, and the rats were observed for clonic seizures of >5-s duration within 60 s. Rats not exhibiting clonic seizures were considered to be protected. Significance between the diazepam group and the interaction group was determined by Fisher Exact Probability Test (HP97/#TS037).

Antagonism of Diazepam-Induced Rotorod Deficit. Male rats were screened on a rod rotating at 16 rpm. They were given a range of doses of antagonist po and 30 min later, diazepam (30 mg/kg ip). For each dose, 6–10 rats were used. After 30 min they were challenged on the rotating bar. Each rat was allowed three trials to remain on the bar for 30 s. Those rats unable to maintain themselves on the rotating bar for the required 30 s were considered to have neurological deficit. In another protocol, animals received 4-h pretreatment with drug followed by diazepam (30 mg/kg po) 1 h before the challenge.

Antagonism of Diazepam-Induced Discriminative Stimuli. The ability of the antagonist to block diazepam (10 mg/kg po) discriminative stimuli was determined in rats as described by Bennett et al.[25]

[^{3}H]Flunitrazepam Binding to the BZ Receptor Complex. The [^{3}H]FNZ binding procedure was modified to allow the study of drugs interacting with the BZ binding site linked to the GABA-A receptor and chloride channel at 21 °C as described by Bennett et al.[25] and by Tallman et al.[26]

Binding of [^{3}H]FNZ to the BZ receptor complex was measured by modification of the methods of Braestrup and Squires,[21] Williams and Risley,[44a] and Squires et al.[44b] Forebrains were removed from male Sprague–Dawley rats (Mbf:SD) (Marland Breeding Farms) following decapitation and were stored at −80 °C. After thawing, the tissues were homogenized in 50 volumes of 50 nM Tris-HCl (pH 7.3, 25 °C) with a Polytron (setting 6 for 30 s). Membranes were sedimented at 48000g for 10 min. Pellets were rinsed three times by resuspension and centrifugation as above. After the first resuspension, membranes were incubated for 30 min at 0 °C. After the third wash, the membrane suspension was frozen at −20 °C for at least 16 h. Immediately before the assay, membrane suspensions were thawed, centrifuged, and washed twice as described above. The final pellet was resuspended in 200 volumes (original tissue weight) of 50 mM Tris-HCl buffer (pH 7.3, 25 °C) containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$. Cold membrane suspensions (2 mL) containing the equivalent of 10 mg of fresh brain tissue were added to triplicate test tubes containing appropriate concentrations of test drugs together with either 0.2 nM [^{3}H]FNZ with or without 10 μM GABA. The samples were incubated at 21 °C for 90 min, filtered through Whatman GF/B microfilter disks (2.4 cm diameter), and washed with three 5-mL portions of ice-cold 50 mM Tris buffer (pH 7.3, 25 °C). Filters were then placed in polyethylene counting vials together with 3.5 mL of Scinti-Verse II, left to diffuse overnight, and counted by conventional liquid scintillation counting. Nonspecific binding was defined as follows: [^{3}H]FNZ, binding in the presence of 10 μM of diazepam or clonazepam. IC_{50} values obtained for 1 (n = 3) were 0.37 ± 0.04 nM without GABA and 0.45 ± 0.05 with GABA to give a GABA ratio of 0.82.

Chemistry. All new compounds indicated by "C, H, N" had microanalytical values within 0.4 unit and exhibited IR and NMR spectra consistent with their structures. Details of the spectra are mentioned for key examples. Proton NMR were determined on a Varian EM-390 instrument with tetramethylsilane as internal standard in deuterated dimethyl sulfoxide, unless othewise stated. IR spectra taken in Nujol mulls were recorded on a Perkin-Elmer Model 457 spectrometer. Melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus or, if above 250 °C, on a Reichert hot-stage apparatus. Mass spectra were taken with a Hewlett-Packard 5985B mass spectrometer either in the CI or the EI mode.

3-(Trifluoromethyl)[1,2,4]triazolo[3,4-*a*]phthalazine (4a). 1-Hydrazinophthalazine hydrochloride (HCl salt of **3**) (30 g, 0.15 mol) was suspended in trifluoroacetic acid (200 mL) with stirring at ca. 35 °C, treated cautiously with trifluoroacetic anhydride (30 mL), and stirred at reflux for 18 h. As the salt gradually dissolved, HCl gas was evolved. The amber-colored solution was evaporated under water vacuum at 70 °C to a syrup which was dissolved in chloroform, washed with 10% aqueous potassium carbonate several times and then with water, dried over sodium sulfate, and concentrated to dryness at reduced pressure. The residual white solid (37.1 g) was recrystallized from toluene to afford colorless plates (31.7 g, 89%): mp 203–204 °C (lit.[45] mp 309–310 °C [sic]); NMR δ 8.0–8.7 (m, 4 H (aromatic)), 9.3 (s, H at 6-position); IR 1518, 1262, 1183, 1147 cm^{-1}; MS m/z 239 (M + 1). Anal. ($C_{10}H_5F_3N_4$) C, H, N.

3-(*p*-Chlorophenyl)[1,2,4]triazolo[3,4-*a*]phthalazine (4d). 1-Hydrazinophthalazine[4] (**3**) (8 g, 0.05 mol) in tetrahydrofuran (40 mL) was treated dropwise with 10 N sodium hydroxide (5.1 mL) and *p*-chlorobenzoyl chloride (8.89 g) in tetrahydrofuran (20 mL) at ambient temperature simultaneously to maintain a near neutral pH and then heated at 80 °C over 15 min. The precipitated solid was refluxed in 2-methoxyethanol and then evaporated to give the desired product. It was recrystallized from ethanol to afford the pure product (5.9 g, 41%); mp 224–225 °C (lit.[46] mp 228–230 °C); NMR δ 7.65–8.7 (m, 8 H (aromatic)), 9.25 (s, H at 6-position); IR 1484, 1377 cm^{-1}; MS m/z 281 (M + 1). Anal. ($C_{15}H_9ClN_4$) C, H, N.

3-Phenyl[1,2,4]triazolo[3,4-*a*]phthalazine (4c). A mixture of 1-hydrazinophthalazine hydrochloride[4] (110 g, 0.51 mol),

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benzaldehyde (53.5 g, 0.51 mol), and methanol (1.2 L) was heated under nitrogen at reflux overnight, concentrated to ca. 250 mL at reduced pressure, and then treated with 1 N sodium bicarbonate (520 mL) with vigorous stirring. The yellow solid was collected, washed with water (3 × 300 mL) and then with ether (2 × 200 mL), and vacuum oven dried at 80 °C over 3 days. The hydrazone, obtained in quantitative yield, mp 180–182 °C (lit.[4] mp 177–178 °C) (98 g, 0.39 mol) was stirred in a mixture of glacial acetic acid (2 L) and anhydrous sodium acetate (145 g), treated dropwise with bromine (24 mL) in acetic acid (100 mL), and then stirred overnight under nitrogen at 90 °C. It was concentrated at reduced pressure to incipient dryness, suspended in cold water (1 L), and neutralized with 5 N sodium hydroxide. The product was washed with water and vacuum oven dried to afford 95 g (99%) of product of suitable purity. A sample was recrystallized from ethanol–ethyl acetate to afford the analytical sample: mp 210–212 °C (lit.[4] mp 208–209 °C). Anal. ($C_{15}H_{10}N_4$) C, H, N.

3-(3-Pyridyl)[1,2,4]triazolo[3,4-*a*]phthalazine (4e) was prepared essentially as described for **4c** in 91% yield, mp 210–212 °C (lit.[8] mp 216–217 °C), and characterized as the hydrochloride salt, mp 261–264 °C (lit.[8] mp 240–242 °C). Anal. ($C_{14}H_{10}ClN_5$) C, H, N.

3-(2-Cyanophenyl)-5-(trifluoromethyl)-2*H*-1,2,4-triazole (5a) was prepared from **4a** and ethanolic potassium hydroxide essentially by the general procedure of Potts and Lovelette,[47] except that the crude product was further purified by dissolution in saturated sodium bicarbonate, followed by a chloroform wash and acidification of the alkaline layer with acetic acid. The precipitated solid (3.6 g, 67% yield, mp 117–120 °C after vacuum oven drying) was recrystallized from benzene to afford the pure sample: mp 120–123 °C; IR 3070, 2228, 1601, 1213, 1187, 1145, 1002, 988 cm^{-1}; NMR δ 7.7–8.15 (m); MS *m/z* 239 (M + 1). Anal. ($C_{10}H_5F_3N_4$) C, H, N. Through the use of sodium methoxide in ethanol as the basic medium, **5c** was obtained from **4c**[4] as a yellow glass [mp 144–147 °C; IR 3320, 2215 cm^{-1}; NMR δ 7.6–8.5 (m, aromatic + N*H*) (99% yield, used without purification)], **5d** from **4d** as a white solid after recrystallization from ethanol and 2-propanol containing HCl [mp 236–238 °C (83%). Anal. ($C_{15}H_9ClN_4$) C, H, N], and **5e** from **4e** as a tan solid (83%), characterized as the *p*-toluenesulfonate salt [mp 196–199 °C (from ethanol). Anal. ($C_{21}H_{17}N_5O_3S$) C, H, N].

2-[5-(Trifluoromethyl)-1,2,4-triazol-3-yl]benzamide (6a). The nitrile **5a** (10.2 g, 0.04 mol) was dissolved in 85% aqueous sulfuric acid (40 mL) at room temperature, heated at 80 °C for 4 h, and quenched in ice. The precipitate was collected, washed with water, and oven dried at 80 °C to give 10.5 g (96%) of amide: mp 218–224 °C. An analytically pure sample was obtained by ethanol recrystallization: mp 224–228 °C; IR 3378, 3334, 1678, 1147 cm^{-1}; NMR 7.6–7.8 (m, 4 H (aromatic)), 7.5 (s, N*H*), 7.9 (s, N*H*), 14.9 (s, N*H*); MS *m/z* 257 (M + 1), 240 (M − NH_2). Anal. ($C_{10}H_7F_3N_4$) C, H, N.

Under similar conditions, **6c** was obtained from **5c** [80 °C, 2 h, then 25 °C, 66 h, 86%, mp 222–225 °C, from ethanol. Anal. ($C_{15}H_{12}N_4O$) C, H, N], **6d** from **5d** [80 °C, 90 min, 92%, mp 271–273 °C, from 2-methoxyethanol). Anal. ($C_{15}H_{11}ClN_4O$) C, H, N], and **6e** from **5e** [80 °C, 2 h, then 25 °C, 5 days, 78%, mp 247–249 °C, from 2-methoxyethanol. Anal. ($C_{14}H_{11}N_5O$) C, H, N].

2-[5-(Trifluoromethyl)-2*H*-1,2,4-triazol-3-yl]benzoic Acid (7). A mixture of the nitrile **5a** (2.38 g, 0.01 mol) and 10 N sodium hydroxide was stirred at 100 °C for 3 h and then concentrated to dryness at reduced pressure. It was triturated with ether, dried, redissolved in water, and acidified with ice-cooling with concentrated hydrochloric acid. The white precipitate was washed with water and dried under vacuum at 120 °C to afford 3.6 g of white solid (2.57 g, 100%, mp ca. 200 °C). Recrystallization from water gave analytically pure product: mp 208–213 °C (lit.[5] mp 207 °C); IR 1690 cm^{-1}; NMR δ 7.6–8.2 (m, 4 H, (aromatic)), (br s, 2 *H*) (exchangeable with D_2O). Anal. ($C_{10}H_6F_3N_3O_2$) C, H, N.

Method 1A. 2-(Trifluoromethyl)[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one (2a). Bromine (9.6 g) was added dropwise at −10 to −5 °C to a solution of sodium hydroxide (7.5 g) in water (80 mL) to form a pale yellow solution. The amide **6a** (12.5 g, 0.049 mol) was added at 0 °C and stirred at 0–10 °C for 30 min. Water (100 mL) was added and the thick mixture heated to 80 °C with stirring until a pale orange-red solution formed. After 1.5 h it was cooled and acidified with glacial acetic acid. The precipitated solid was washed thoroughly with water and vacuum oven dried at 60 °C to afford the crude product (11.4 g, 91%, mp ca. 270 °C). The product was recrystallized from ethanol–water (1:1) and then 95% ethanol to give the pure product, mp 297.5–299.5 °C, after vacuum oven drying (80 °C, 18 h) (lit.[2] mp 295–297 °C): IR 1737, 3160 cm^{-1}. Anal. ($C_{10}H_5F_3N_4O$) C, H, N. A sample (0.5 g) in trifluoroacetic acid (20 mL) was heated 30 min at reflux, evaporated to dryness, and triturated with water to give material identical (IR, melting point, mixture melting point) with the starting material.

2-Phenyl[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one (2c). The amide **6c** (40 g 0.15 mol) was dissolved in dimethylformamide (400 mL), and lead tetraacetate (60.5 g) was added in eight portions over 5 min with stirring. Triethylamine (63 mL) was added and the mixture heated at 80 °C over 1 h. It was quenched in ice-water (2 L), and the white product (35 g) was recrystallized from ethanol to afford the pure product (22 g, 55%), mp 311–313 °C, after vacuum oven drying (80 °C, 16 h): IR 1728, 1696, 3080 cm^{-1}; NMR δ 7.35–8.3 (m, 9 H (aromatic)), 12.3 (s, N*H* (exchanges with D_2O)); MS *m/z* 263 (M + 1); UV 248 (log ε = 4.65), 232 (4.58). Anal. ($C_{15}H_{10}N_4O$) C, H, N.

2-(*p*-Chlorophenyl)[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one (2d) was prepared by the same procedure except that it was recrystallized from a large volume of 2-methoxyethanol: mp 315–318 °C (72%); IR 1751, 1718, 1626, 1598, 1557, 754 cm^{-1}; NMR δ 7.35–8.25 (m, 8 H (aromatic)), 12.3 (s, N*H*); MS *m/z* 297 (M + 1). Anal. ($C_{15}H_9ClN_4O$) C, H, N.

2-(3-Pyridyl)[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one (2e). A solution of amide **6e** (20.5 g, 0.078 mol) dissolved in dimethylformamide (600 mL) was treated with glacial acetic acid (9.4 g) followed by lead tetraacetate (35 g) and heated 66 h at 85 °C under nitrogen with stirring. The dark red mixture was quenched in ice–water overnight and the light brown precipitate collected, dissolved in hot ethanol, filtered through diatomaceous earth (Celite), and concentrated to dryness at reduced pressure. The light brown product (6.5 g, 28%) was characterized as its *p*-toluenesulfonate salt: mp 268–271 °C (from ethanol); IR 1746 cm^{-1}; NMR δ 2.3 (s, CH_3), 7.1–9.5 (m, 12 H (aromatic)), 8.9 (broad, 1 H (exchangeable with D_2O)), 12.4 (s, N*H* (exchangeable)). Anal. ($C_{21}H_{17}N_5O_4S$) C, H, N. Continuous extraction of the aqueous layer with ether over several days produced an additional 6 g of crude product.

Method 1B. 6-Methyl-2-(trifluoromethyl)[1,2,4]triazolo-[1,5-*c*]quinazolin-5(6*H*)-one (2b). A mixture of **2a** (5.1 g, 0.02 mol), sodium methoxide (1.1 g), and dry dimethyl sulfoxide (30 mL) was heated briefly to 60 °C under nitrogen, then cooled to 5 °C, and treated with methyl iodide (1.3 mL). It was stirred 2 h at 80 °C and then quenched in ice–water containing a little sodium bisulfite. The off-white solid was washed with water and the crude product (4.65 g, 83%, mp 222–229 °C) recrystallized twice from ethyl acetate to give an analytical sample: mp 229.5–233.5 °C; IR 1735 cm^{-1}. Anal. ($C_{11}H_7F_3N_4O$) C, H, N.

6-Methyl-2-phenyl[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one (2k) was prepared in the same manner from **2c**, mp 231–234 °C, from tetrahydrofuran (96%): IR 1708, 1622, 1596, 1249, 754, 724 cm^{-1}; NMR δ 8.32 (dd, H at 10), 8.23 (m, *H* at 2′ and 6′), 7.82 (td, *H* at 8), 7.69 (d, *H* at 7), 7.53–7.61 (m, *H* at 3′, 4′, 5′), 7.50 (td, *H* at 9), 3.74 (s, CH_3); UV (MeOH) 233 (log ε = 4.59), 247, (4.65), 310 (3.85). Anal. ($C_{16}H_{12}N_4O$) C, H, N.

6-Methyl-2-(3-pyridyl)[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one (2m) was prepared similarly from **2e** except that sodium hydride was used in place of sodium methoxide. The product was purified as its *p*-toluenesulfonate salt and recrystallized from ethanol: mp 217–219 °C (37%); IR 2600 (br), 1718, 1619, 1242, 1159, 1001, 682 cm^{-1}; NMR δ 9.5 (s, *H* at 2′), 8.9 (dd, 2 H (aromatic)), 7.4–8.0 (m, 6 H (aromatic)), 7.1 (d, 2 H (aromatic)), 7.0 (br s, O*H*), 3.75 (s, NCH_3), 2.3 (s, CCH_3). Anal. ($C_{22}H_{19}N_5O_4S$) C, H, N.

Method 2A. 2-Phenyl[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one (2c). Benzamidine (17.6 g, 0.146 mol) prepared from its hydrochloride hydrate[12] was suspended in chlorobenzene (500 mL), anthranilic acid hydrazide (**11**, X = H) (22.2 g, 0.146 mol)

(47) Potts, K. T.; Lovelette, C. *J. Org. Chem.* **1969**, *34*, 3221.

was added, and the mixture was stirred under nitrogen at reflux for 16 h. After cooling, the product was collected, washed with dry ether (3 × 500 mL), and air-dried to afford **N^1-(2-aminobenzoyl)benzamidrazone** (**9**, R = X = H) (18 g, 48%, mp 200–203 °C). A sample was recrystallized for analysis from 2-methoxyethanol: mp 200–203 °C: IR 3500, 3450, 3350, 3200, 1670, 1640 cm^{-1}. Anal. ($C_{14}H_{14}N_4O$) C, H, N. Compound **9** (1.2 g, 4.9 mmol) in ethyl carbamate (10 g) was heated under nitrogen at 210 °C for 3 h. At 190 °C, it formed a clear colorless melt which turned pale yellow at 210 °C. It was allowed to cool and then stirred over 1 h in water (300 mL) to dissolve residual ester. The white solid was collected, washed thoroughly with water and 2-propanol, and air-dried to give **2c** (1.0 g, 84%), identical with the material prepared by method 1A.

Method 2B. 9-Chloro-2-(2-pyridyl)[1,2,4]triazolo[1,5-c]quinazolin-5(6*H*)-one (2i). A mixture of 2-pyridylamidrazone (mp 89–92 °C, prepared as described by Case,[10] 6.9 g, 0.051 mol), 5-chloroisatoic anhydride (6-chloro-1,2-dihydro-4*H*-3,1-benzoxazine-2,4-dione) (10 g, 0.051 mol), and pyridine (150 mL) was stirred at room temperature under nitrogen overnight. The reaction mixture was diluted with ether (200 mL) and the solid collected, triturated with ethanol, and air-dried to give ***N*-(2-amino-5-chlorobenzoyl)-2-pyridylamidrazone (9i)** (8.2 g, 56%, mp 225–230 °C, IR 1635 cm^{-1}). The amidrazone **9i** was suspended in a 73.5/26.5 w/w mixture of diphenyl ether and biphenyl (90 mL), heated under nitrogen at 180 °C over 3 h, allowed to cool, and poured into hexane (250 mL). The yellow product (7.1 g, 91%, mp 194–197 °C) was recrystallized from absolute ethanol to give pure **3-(2-amino-5-chlorophenyl)-5-(2-pyridyl)-2*H*-1,2,4-triazole (10i)**: mp 207–209 °C; IR 3320, 1610, 1593, 1505 cm^{-1}. Anal. ($C_{13}H_{10}ClN_5$) C, H, N. A mixture of **10i** (10.3 g, 37.9 mmol) and ethyl carbamate (30 g) was gradually heated to 200 °C, and after 2.5 h it was cooled and the solid stirred vigorously in water (300 mL) over 1 h. After drying 20 h under vacuum at 70 °C, **2i** was obtained pure (9.9 g, 88%, mp >340 °C); IR 3360, 1760, 1740 cm^{-1}; NMR δ 7.6–9.3 (m, 7 H (aromatic)), 13.2 (s, N*H*). Anal. ($C_{14}H_8ClN_5O$) C, H, N.

9-Chloro-2-(3-pyridyl)[1,2,4]triazolo[1,5-c]quinazolin-5(6*H*)-one (2l), prepared from 3-pyridylamidrazone, mp 72–75 °C, by a similar route, was obtained crude in 92% overall yield and purified as the *p*-toluenesulfonate salt, mp 320–322 °C, in 21% yield: IR 1746 cm^{-1}1; NMR δ 2.25 (s, C*H*$_3$), 7.1–8.2 (m, 9 H (aromatic)), 8.9–9.05 (m, 2 H (aromatic)), 9.45 (s, 1 H (2′-H)), 8.4–9.3 (br s (acidic *H*)), 12.4 (s, N*H*). Anal. ($C_{21}H_{16}ClN_5O_4S$) C, H, N.

Method 2B. 9-Chloro-2-phenyl[1,2,4]triazolo[1,5-c]quinazolin-5(6*H*)-one (2g). 5-Chloroisatoic anhydride (20 g, 0.1 M) suspended in absolute ethanol (200 mL) was treated with HCl gas with stirring at ambient temperature until a clear solution was obtained. It was concentrated to incipient dryness and treated with dry ether to produce **ethyl 5-chloroanthranilate hydrochloride** (23 g, 96%, mp 148–151 °C, (lit.[48] mp 146–148 °C). This was combined with hydrazine hydrate (200 mL) in ethanol (200 mL), stirred at reflux over 16 h, concentrated to ca. 200 mL, and diluted with water (300 mL). The white precipitate was vacuum oven dried to afford **5-chloroanthranilic acid hydrazide** (**11**, X = 5-Cl) (16.7 g, 92%, mp 129–134 °C). Benzamidine hydrochloride hydrate (4.64 g, 30 mmol) was dissolved in absolute ethanol (110 mL) and treated with a solution of sodium hydroxide (1.2 g) in water (1.2 mL), and the precipitated salt was filtered off. The solution of the amidine was added to the hydrazide (5 g, 27 mmol) in a 9:1 mixture of chlorobenzene and ethanol (200 mL) and refluxed in an apparatus containing a solvent separator. After 130 mL of solvent had been removed, the solution was cooled and treated with dry ether to precipitate **3-(2-amino-5-chlorophenyl)-5-phenyl-1,2,4-triazole (10g)** (4.8 g, 62%, mp 254–255 °C, lit.[12] mp 257–258 °C). A mixture of **10g** (7 g, 25.8 mmol) in dioxane (100 mL) was treated with trichloromethyl chloroformate (5.11 g, 25.8 mmol) with stirring. After 20 min, triethylamine (2.62 g) was added and the mixture stirred under nitrogen for 20 h. It was stirred 1 h longer at reflux to complete the reaction. On cooling, an off-white precipitate formed. It was washed thoroughly with ether, triturated with water, and dried at 70 °C under vacuum to yield the desired product (5.4 g, 71%) which sublimed at 270 °C but did not melt up to 340 °C: IR 3260, 1732 cm^{-1}; NMR δ 7.5–8.5 (m, 8 H (aromatic)), 12.7 (s, N*H* (exchangeable with D_2O)). Anal. ($C_{15}H_9ClN_4O$) C, H, N.

Method 3A. 2-(2-Fluorophenyl)[1,2,4]triazolo[1,5-c]quinazolin-5(6*H*)-one (2p). To a vigorously stirring mixture of anthranilonitrile hydrochloride (15.5 g, 0.1 mol) in dry dioxane (200 mL) under nitrogen was added dropwise trichloromethyl chloroformate (6.3 mL) in dioxane (20 mL) and the mixture stirred under nitrogen at 60 °C for 18 h. It was filtered and the precipitate washed with dry ether and discarded. The filtrate and washings were evaporated under vacuum, and the residual solid was taken up in boiling hexane (250 mL) and filtered hot. On cooling, **2-isocyanatobenzonitrile** (3.95 g, 30%) was obtained, mp 60–62 °C (lit.[49] mp 61 °C). This nitrile (2.9 g, 0.02 mol) and 2-fluorobenzhydrazide (3.1 g, 0.02 mol) in dioxane (80 mL) were stirred under nitrogen at 80–90 °C for 3 h and evaporated to dryness at reduced pressure. Trituration with methanol produced solid in two crops (4.65 g, mp >300 °C) which was a mixture containing uncyclized material. A portion (3.0 g) was suspended in ethanol (55 mL), treated with concentrated ammonium hydroxide (20 mL), and stirred 2 h at 80 °C. A precipitate formed and the cooled mixture yielded 2.5 g of white solid, mp 323–324 °C (69% from the isocyanate). Two recrystallizations from 2-methoxyethanol gave the analytical sample: mp 326–329 °C; MS *m/z* 281 (M + 1); IR 3177, 1730, 1695 cm^{-1}; NMR δ 7.35–8.3 (m, 8 H (aromatic)), 12.35 (s, N*H*). Anal. ($C_{15}H_9FN_4O$) C, H, N.

Method 3B. 9-Chloro-2-(2-furyl)[1,2,4]triazolo[1,5-c]quinazolin-5(6*H*)-one (2f). 5-Chloro-2-isocyanatobenzonitrile (2.7 g, 15 mmol) dissolved in warm toluene (100 mL) was treated with dimethylamine in toluene (17.6%, 20 mL) over 20 h. It was concentrated to dryness at reduced pressure and recrystallized from cyclohexane to give white crystals of ***N*,*N*-dimethyl-*N*′-(4-chloro-2-cyanophenyl)urea (14)** (2.1 g, 71%): mp 95–97 °C; IR 3430, 2205, 1680 cm^{-1}. Anal. ($C_{10}H_{10}ClN_3O$) C, H, N. The urea (1.79 g, 8 mmol) was dissolved in 2-methoxyethanol (25 mL), 2-furoylhydrazine (1.05 g, 8 mmol) was added, and the solution was refluxed 66 h under nitrogen. The white solid obtained after cooling, washing with methanol, and drying under vacuum (2.01 g, 88%, mp >340 °C) was identical (IR, NMR) with a sample of **2f** prepared by a different route.[13]

Method 3C. 9-Chloro-2-(2-fluorophenyl)[1,2,4]triazolo-[1,5-c]quinazolin-5(6*H*)-one (2r). To a mixture of 5-chloroanthranilonitrile (15.6 g, 0.1 mol), 2-butanone (300 mL), and sodium bicarbonate (10 g) was added methyl chloroformate (8.4 mL), and the mixture was heated 18 h at 80 °C under nitrogen. It was cooled and filtered and the precipitate washed with 2-butanone. The combined filtrates were concentrated to dryness at reduced pressure and recrystallized from chlorobenzene–cyclohexane to give pure **5-chloro-2-[(methoxycarbonyl)amino]benzonitrile** (**15**, R = Me) (16 g, 76%): mp 127–132 °C; IR 3400, 2215, 1725 cm^{-1}; NMR δ 3.7 (s, C*H*$_3$), 7.6–8.35 (m, 3 H (aromatic)), 10.1 (s, N*H*). Anal. ($C_9H_7ClN_2O_2$) C, H, N. A mixture of this urethane (4.2 g, 0.02 mol), 2-fluorobenzhydrazide (3.1 g), and 2-methoxyethanol (100 mL) was stirred at reflux under nitrogen over 7 h. It was concentrated to dryness, but since the IR of the residue still showed urethane present, it was taken up in 2-methoxyethanol (80 mL) containing tri-*n*-propylamine (0.3 mL) and heated at reflux for 20 h. Solvent (10 mL) was distilled off and the residue allowed to cool to afford hairlike needles (4.1 g, after vacuum oven drying at 90 °C, 65%, mp >340 °C): IR 3150, 1750 cm^{-1}. Anal. ($C_{15}H_8ClFN_4O$) C, H, N.

2-(2-Aminophenyl)-5-phenyl-1,3,4-oxadiazole. A mixture of anthranilic acid hydrazide (**11c**) (10 g, 0.066 mol) and benzamidine hydrochloride hydrate (10.4 g) in 2-methoxyethanol (200 mL) was refluxed in a Soxhlet apparatus containing 3A molecular sieves over 5 days under nitrogen. The crude product showed a single spot in TLC, which fluoresced differently under UV light from the corresponding 1,2,4-triazole.[12] The mixture was quenched in water (1 L) and the precipitated solid was recrystallized from ethanol–water to give the pure product (7.5 g, 48%, mp 161–163 °C): IR 3450, 3350, 1630, 1610 cm^{-1}; NMR δ 6.6–8.3 (m, 9 H

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(aromatic), and 2 H (exchangeable with D_2O)). Anal. ($C_{14}H_{11}N_3O$) C, H, N.

2-Phenyl[1,2,4]triazolo[1,5-*c*]quinazoline (16). A mixture of 3-(2-aminophenyl)-5-phenyl-1,2,4-triazole[12] (9.3 g, 40 mmol), triethyl orthoformate (500 mL), and potassium carbonate (7 g) was refluxed 20 h under nitrogen. The material was concentrated to dryness, stirred 1 h with water (500 mL), collected, and recrystallized from 2-propanol to give white needles (4.2 g, 43%, mp 198–200 °C): IR 1625, 1603, 1520, 902, 723, 690 cm^{-1}; NMR δ 7.5–8.6 (m, 9 H (aromatic)), 9.7 (s, *H* at 5-position); UV 249 (log ϵ 4.71). Anal. ($C_{15}H_{10}N_4$) C, H, N.

5-Methyl-2-phenyl[1,2,4]triazolo[1,5-*c*]quinazoline (17). Acylamidrazone **9** (R = X = H) (6 g, 25 mmol) was heated with ammonium acetate (40 g) in an apparatus containing a water separator at 140 °C over 4 h. After 20 mL of liquid was removed, additional ammonium acetate (15 g) was added and heating continued for 4 h. The thick paste was quenched in water (500 mL) and the precipitate collected and recrystallized from tetrahydrofuran and water to give the pure product (5.3 g, 82%, 204–206 °C); IR 1635, 792, 777, 722, 692 cm^{-1}; NMR δ 3.5 (s, CH_3), 7.6–8.9 (m, 9 H (aromatic)). Anal. ($C_{16}H_{12}N_4$) C, H, N.

2,5-Diphenyl[1,2,4]triazolo[1,5-*c*]quinazoline (18). A mixture of 3-(2-aminophenyl)-5-phenyl-1,2,4-triazole[12] (5 g, 21 mmol), benzoic acid (20 g), and diphenyl ether (40 mL) was stirred under nitrogen for 36 h at 190–200 °C. The cooled mixture was filtered and the precipitate washed thoroughly with petroleum ether. It was taken up in methylene chloride, washed with dilute aqueous sodium hydroxide and then with water, dried over sodium sulfate, and concentrated to dryness to give 4.76 g (70%) of a white solid. Recrystallization from methylene chloride–cyclohexane gave the analytical sample: mp 171–173 °C (lit.[16] mp 170 °C); IR 1626, 1607, 1521, 732, 687 cm^{-1}; NMR δ 7.45–8.7 (m (aromatic)); UV (EtOH) 299 (log ϵ = 4.2), 257 (4.7) [lit.[16] UV 300 (3.8)]; MS *m/z* 323 (M^+). Anal. ($C_{21}H_{14}N_4$) C, H, N.

5-Chloro-2-phenyl[1,2,4]triazolo[1,5-*c*]quinazoline (19). A mixture of **2c** (1.3 g, 50 mmol) and phosphoryl chloride (30 mL) was treated dropwise with pyridine (0.8 mL) at room temperature and then heated at 100 °C under nitrogen for 20 h. It was concentrated to dryness at reduced pressure, taken up in ethyl acetate, washed with 6% aqueous HCl, dried over sodium sulfate, and concentrated to a white solid (0.9 g, mp 195–199 °C, 64%). Recrystallization from ethyl acetate gave the pure product: mp 199–201 °C: IR 1625, 1600, 1518, 772, 723 cm^{-1}; NMR δ 7.55–8.55 (m (aromatic)). Anal. ($C_{15}H_9ClN_4$) C, H. N.

9-Chloro-2-phenyl[1,2,4]triazolo[1,5-*c*]quinazolin-5-amine (20). Cyanogen bromide (1.5 g, 14 mmol) was added to a solution of 3-(2-amino-5-chlorophenyl)-5-phenyl-1,2,4-triazole[12] (3.8 g, 14 mmol) in methanol (100 mL) and the mixture refluxed 4 h under nitrogen. Triethylamine (2.8 mL, 28 mmol) was added through the condenser and reflux continued 3 h. It was allowed to cool to room temperature and the precipitate was collected and stirred vigorously in water overnight. The product (1.9 g, 46%, mp 284–286 °C) was analytically pure: IR 3444, 3088, 1684, 814, 725, 689 cm^{-1}; NMR δ 7.5–7.75 (m 5 H (aromatic)), 8.0 (s, NH_2, exchangeable with D_2O), 8.2–8.4 (m, 3 H (aromatic)). Anal. ($C_{15}H_{10}ClN_5$) C, H, N.

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Registry No. **2a**, 58022-42-7; **2b**, 130408-05-8; **2c**, 104614-81-5; **2d**, 104614-80-4; **2e**, 104615-00-1; **2e** *p*-toluenesulfonate, 130408-10-5; **2f**, 104614-82-6; **2g**, 104614-95-1; **2h**, 104614-90-6; **2h** *p*-toluenesulfonate, 130408-13-8; **2i**, 104614-94-0; **2j**, 104631-44-9; **2k**, 104614-85-9; **2l**, 104614-92-8; **2l** *p*-toluenesulfonate, 130408-11-6; **2m**, 104614-88-2; **2m** *p*-toluenesulfonate, 130408-12-7; **2n**, 104615-38-5; **2o**, 130408-06-9; **2p**, 104615-05-6; **2q**, 130408-07-0; **2r**, 104615-04-5; **2s**, 104615-02-3; **2t**, 104614-97-3; **2u**, 104614-96-2; **2v**, 104614-98-4; **2x**, 104615-03-4; **2y**, 104614-99-5; **2z**, 130408-08-1; **2z** *p*-fumarate, 130408-14-9; **2aa**, 104615-07-8; **2bb**, 130408-09-2; **2cc**, 87611-10-7; **3**, 86-54-4; **3**·HCl, 304-20-1; **4a**, 53551-55-6; **4c**, 70591-70-7; **4d**, 94445-81-5; **4e**, 97193-59-4; **5a**, 130407-95-3; **5c**, 130407-96-4; **5d**, 104615-51-2; **5e**, 130407-97-5; **6a**, 130407-98-6; **6c**, 104615-52-3; **6d**, 104615-50-1; **6e**, 104615-53-4; **7**, 30481-70-0; **9**, 130407-99-7; **9i**, 130408-00-3; **10g**, 104615-59-0; **11c**, 1904-58-1; **14**, 104615-88-5; **15**, 104615-85-2; **16**, 130408-02-5; **17**, 130408-03-6; **18**, 61330-43-6; **19**, 130408-04-7; **20**, 104615-17-0; ethyl 5-chloroanthranilate hydrochloride, 130408-01-4; 5-chloroanthranilic acid hydrazide, 5584-15-6; 2-isocyanatobenzonitrile, 42066-86-4; *p*-chlorobenzoyl chloride, 122-01-0; benzaldehyde (1-phthalazine)hydrazone, 67073-46-5; benzamidine hydrochloride, 1670-14-0; 5-chloroisatoic anhydride, 20829-96-3; 2-pyridylamidrazone, 1005-02-3; 3-(2-amino-5-chlorophenyl)-5-(2-pyridyl)-2*H*-1,2,4-triazole, 104615-57-8; 3-pyridylamidrazone, 98495-32-0; anthranilonitrile hydrochloride, 6944-57-6; 2-fluorobenzhydrazide, 2368-80-1; 5-chloro-2-isocyanatobenzonitrile, 64411-72-9; 2-furoylhydrazine, 3326-71-4; 5-chloroanthranilonitrile, 5922-60-1; 2-(2-aminophenyl)-5-phenyl-1,3,4-oxadiazole, 23047-95-2; 3-(2-aminophenyl)-5-phenyl-2*H*-1,2,4-triazole, 25518-15-4; 3-(2-amino-5-chlorophenyl)-5-phenyl-2*H*-1,2,4-triazole, 104615-59-0.