mixture was refluxed for 20 h. Volatiles were removed under reduced pressure; the residue was dissolved in $CHCl_3$ (100 mL) and added to ice–water. The layers were separated, and the aqueous layer was extracted with chloroform (2 × 200 mL). The combined extract was washed with 5% $NaHCO_3$ (2 × 120 mL) followed by brine (2 × 50 mL). It was dried over $MgSO_4$ and filtered, and the volatiles were removed. The residue was crystallized from chloroform–hexane, affording 1.78 g of 4-chloro-1-(trifluoromethyl)[1,2,4]triazolo[4,3-*a*]quinoxaline (VI): mass spectrum, *m/e* 272 (M^+).

c. *N*-Cyclopentyl-1-(trifluoromethyl)[1,2,4]triazolo[4,3-*a*]quinoxalin-4-amine (9). A solution of 4-chloro-1-(trifluoromethyl)[1,2,4]triazolo[4,3-*a*]quinoxaline (VI) (0.6 g, 0.002 mol) and cyclopentanamine (1.0 g, 0.011 mol) in 10 mL of DMF was stirred at room temperature for 20 h and then added to ice–water. Precipitated solid was filtered, dissolved in 100 mL of chloroform, washed with brine (1 × 25 mL), dried over $MgSO_4$, and filtered, and the volatiles were removed. The residue was dissolved in ether–2-propanol and diluted with hexane. Solid material obtained was filtered and dried, affording 0.42 g (60%) of *N*-cyclopentyl-1-(trifluoromethyl)[1,2,4]triazolo[4,3-*a*]quinoxalin-4-amine: mp 183–184 °C; mass spectrum, *m/e* 321 (M^+). Anal. ($C_{15}H_{14}N_5F_3$) C, H, N, F.

Receptor Binding. A_1 binding was carried out with [^{3}H]CHA in rat whole brain membranes,[4] and A_2 binding was carried out with [^{3}H]NECA in the presence of 50 nM unlabeled N^6-cyclopentyladenosine in rat striatal membranes.[4]

Acknowledgment. We thank James Fergus and Gina Lu for providing biochemical screening results.

Registry No. I (R_1 = 2-Pr, R^2 = R_3 = H), 91895-47-5; I (R_1 = 2-Pr, R^2 = H, R_3 = Et), 91895-54-4; I (R_1 = Et, R_2 = Et, R_3 = H), 91895-45-3; **I** (R_1 = Cyclopentyl, R_2 = R_3 = H), 113181-11-6; I (R_1 = cyclopentyl, R_2 = H, R_3 = CH_3), 113181-12-7; I (R_1 = cyclopentyl, R_2 = H, R_3 = Et), 113181-13-8; I (R_1 = cyclopentyl, R_2 = H, R_3 = Pr), 113181-14-9; **I** (R_1 = cyclopentyl, R_2 = H, R_3 = $H_3C(CH_2)_3$, 113181-15-0; **I** (R_1 = cyclopentyl, R_2 = H, R_3 = CF_3), 113181-16-1; **I** (R_1 = cyclopropyl, R_2 = H, R_3 = Et), 113181-17-2; I (R_1 = cyclobutyl, R_2 = H, R_3 = Et), 113181-18-3; **I** (R_1 = cyclohexyl, R_2 = H, R_3 = Et), 113181-19-4; **I** (R_1 = *exo*-2-norbornyl, R_2 = H, R_3 = Et), 113181-20-7; **I** (R_1 = phenyl, R_2 = H, R_3 = Et), 113181-21-8; **I** (R_1 = (*S*)-$H_3CCH(OH)CH_2$, R_2 = H, R_3 = Et), 113181-22-9; **III**, 91895-39-5; **IVc**, 91895-40-8; **IVd**, 91895-41-9; **IV** (R_3 = H), 62603-54-7; **IV** (R_3 = $H_3D(CH_2)_3$), 113181-23-0; **V**, 91895-67-9; **VI**, 91895-68-0; $C_6H_5NH_2$, 62-53-3; (*S*)-$H_3CCH(OH)CH_2NH_2$, 2799-17-9; $CH(OEt)_3$, 122-51-0; $H_3C(OEt)_3$, 78-39-7; $Et(OEt)_3$, 115-80-0; $Pr(OEt)_3$, 24964-76-9; $PrCH_2(OEt)_3$, 919-29-9; cyclopentylamine, 1003-03-8; cyclopropylamine, 765-30-0; cyclobutylamine, 2516-34-9; cyclohexylamine, 108-91-8; *exo*-2-aminonorbornane, 7242-92-4; adenosine, 58-61-7.

Structure–Activity Profile of a Series of Novel Triazoloquinazoline Adenosine Antagonists

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During a search for benzodiazepine receptor modulators, a highly potent adenosine antagonist (CGS 15943) was discovered. The compound was defined as a resonance-stabilized hybrid of the canonical structures 9-chloro-2-(2-furyl)[1,2,4]triazolo[1,5-*c*]quinazolin-5-amine (**2a**) and 9-chloro-2-(2-furyl)-5,6-dihydro[1,2,4]triazolo[1,5-*c*]-quinazolin-5-imine (**2b**). Spectroscopic evidence and chemical reactivity in polar media favor the amine form **2a** as the major contributor of the two canonical structures. The synthesis of **2** and some of its analogues and the structure–activity relationships in four biological test systems are described. Replacement of the 9-chloro group by hydrogen, hydroxyl, or methoxyl gave compounds with comparable binding potency at the A_1 and A_2 receptors but much less activity as antagonists of 2-chloroadenosine in guinea pig tracheal strips. Alkylation of the 5-amino group caused, in general, a loss of binding activity, particularly at the A_2 receptor, as well as complete loss of activity in the tracheal model. Modification of the 2-furyl group caused a pronounced loss of activity in all of the test systems.

The discovery of CGS 8216 (**1**) in these laboratories as a potent benzodiazepine receptor antagonist[1,2] led to the screening of other tricyclic heterocyclic structures for similar activity coupled with a search for an understanding of the mechanism of action of this novel compound. In 1979, Phillis and co-workers reported that theophylline, an adenosine antagonist,[3] antagonized the depressant action of flunitrazepam on cerebral cortical neurons in rats.[4] Other investigators had reported that theophylline and other xanthines block diazepam binding sites in brain tissue. Furthermore, inosine, an adenosine metabolite, interacted with brain benzodiazepine receptors.[5,6] These observations led to the suggestion that benzodiazepines and adenosine depress central neurons by acting at the same receptor. A comparison of **1** and theophylline in the adenosine-stimulated adenylate cyclase system present in guinea pig synaptoneurosomes[7] revealed that **1** indeed blocked adenosine activation more potently than theophylline.[2] Accordingly, this test system was used in screening other chemical structures prepared as potential anxiomodulators. Subsequently, the triazoloquinazoline structure **2** (CGS 15943) was discovered to be more potent than any adenosine antagonist reported at that time (January, 1983). It was approximately 500 times as active as theophylline and 250 times as potent as **1**.

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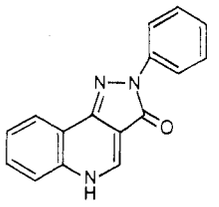
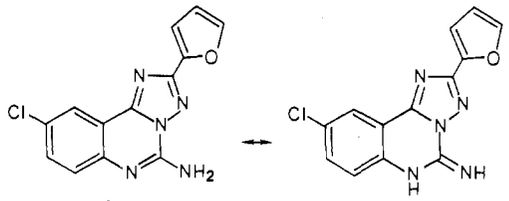


1



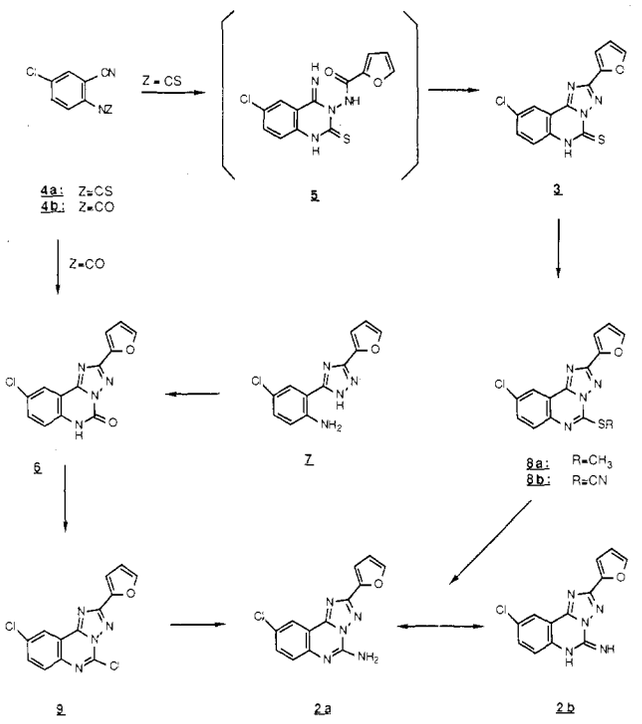
2a 2b

Theophylline, caffeine, and other xanthines have attracted interest over several decades due to a variety of pharmacological properties including central stimulation, diuresis, antiasthmatic, and cardiotonic effects. A renewed and expanded interest over the last decade[8] coincided with the characterization of different adenosine receptor sites, in particular the high-affinity receptor that can inhibit adenylate cyclase (A_1) and the low-affinity receptor stimulatory to adenylate cyclase (A_2). Modification of the substituents in the xanthine structure **2** has produced compounds far more potent than theophylline as measured by activity at these binding sites. Two recent examples are PACPX[9,10] and XAC.[11]

Since many of the xanthines show phosphodiesterase inhibition and calcium mobilizing effects,[12] there is interest in finding other structural types with potent adenosine antagonist activity without phosphodiesterase inhibiting properties. Some non-xanthine heterocycles reported to have adenosine antagonist activity are alloxazine, a benzo[*g*]pteridine,[13] 9-substituted adenines such as 9-methyladenine,[13] the pyrazolo[3,4-*b*]pyridines etazolate, cartazolate, and tracazolate,[14] the pyrazolo[3,4-*d*]pyrimidines, particularly DJB-KK,[15,16] and certain pyrazolo-[4,3-*d*]pyrimidin-7-ones.[17]

In this paper, we describe the synthesis of **2** with some of its analogues and compare the structure–activity relationships (SAR) in (a) A_1 and A_2 receptor binding assays, (b) a screen for the inhibition of adenosine-stimulated adenylate cyclase in guinea pig synaptoneurosomes, and (c) an in vitro model for measuring the antagonism of 2-chloroadenosine-induced relaxation in histamine-contracted guinea pig trachea. More detailed biochemical and pharmacological studies on **2** have been reported separately.[18,19]

Scheme I



Chemistry. The 5-aminoid 2-substituted [1,2,4]triazolo[1,5-*c*]quinazolines were prepared by two different procedures. The first method involved displacement of a favorable leaving group from the 5-position of the heterocycle, either the 5-methylmercapto moiety (method 1A), the 5-isothiocyanato group (method 1B), or the 5-chloro-substituent (method 1C) by an amine. A second method, the ring closure of a 5-(*o*-aminophenyl)-3-substituted-1*H*-1,2,4-triazole with cyanogen bromide (method 2A) or cyanamide (method 2B) produced only 5-amino (or 5-imino-5,6-dihydro) compounds. All of these methods were used to prepare the lead compound **2** as illustrated in Scheme I.

The key thiono compound **3** was prepared by a novel synthetic route. Treatment of the isothiocyanate **4a** prepared from 5-chloroanthranilonitrile and thiophosgene, with 2-furoic acid hydrazide preferably in a polar, nonhydroxylic solvent such as dimethylacetamide or *N*-methyl-2-pyrrolidinone at temperatures above 100 °C, led to the tricyclic thiono compound **3** in one step. This double cyclization is reminiscent of the work of Papadopoulus, who found that anthranilonitrile reacted smoothly with 2-chloroethyl isocyanate to form a urea, which, on warming with an alcohol under basic conditions, produced 2,6-dihydroimidazo[1,2-*c*]quinazolin-5(3*H*)-one in excellent yield.[20] The formation of intermediate **5** in our synthesis seems likely, but our efforts to isolate and purify this compound resulted in its cyclization. Similarly, the *o*-isocyanatobenzonitrile **4b** reacts with a hydrazide under similar conditions to produce a 5-oxo compound such as **6**. This tricyclic urea was first prepared by reaction of the triazole **7** with the phosgene equivalent trichloromethyl chloroformate. Since the double cyclization occurs so readily, it seems likely that no Dimroth-type rearrange-

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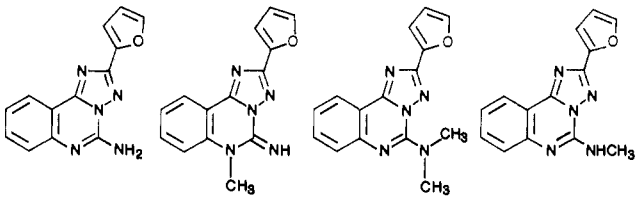
ment[21] occurs, which could lead to the isomeric [1,2,4]-triazolo[4,3-*c*]quinazoline ring system. Furthermore, the cyclization of a hydrazide of 2-chloro-4-hydrazinoquinazoline, which might be expected to give a [1,2,4]-triazolo[4,3-*c*]quinazolin-5(6*H*)-one, is reported to rearrange to a [1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one, the structure of which was confirmed by X-ray crystallography.[22] Many other examples supporting the ease of rearrangement of the [4,3-*c*] to the [1,5-*c*] system have been documented,[23] but the reverse rearrangement has never been reported. The anion of **3** was converted to either the methylthio compound **8a** or the isothiocyanato derivative **8b**. The alkylthio intermediate was converted to the target compound with ammonia/ammonium hydroxide mixture in a sealed vessel or with an amine in a hydroxylic solvent under pressure to produce an N-alkylated target. The isothiocyanato group was readily displaced by ammonia bubbled through a solution in 1,3-dimethyl-2-imidazolidone at room temperature. Alternatively, **6** was converted by phosphoryl chloride/phosphorous pentachloride in pyridine to the 5,9-dichloro compound **9** and thence to the target compound by ammonia treatment. The triazole **7** and other 3,5-diaryltriazoles were prepared by reaction of the requisite anthranilic acid hydrazide with an amidine, the details of which have been reported separately.[24] Alternatively, the triazole **7** was prepared by alkaline hydrolysis of **6** in refluxing 2-methoxyethanol. The conversion of **7** to **2** with cyanogen bromide or cyanamide[25] could also lead to the unwanted [4,3-*c*] ring system if the nitrogen at position 4 of the triazole were attacked and no further rearrangement occurred. Since the structures **3** and **6** appear correct beyond reasonable doubt, the cyclization must lead to the product indicated.

Compound **2** and its 5-N-monosubstituted analogues are probably best depicted as mesomeric hybrids of an amine structure such as **2a** and an imine such as **2b**. The ultraviolet spectra of structures **10** and **13a** were compared with that of compound **11**, in which the **2b** configuration is locked in place, and **2a**, in which the **2a**-type configuration is present. Comparison in acid, neutral, and basic media (Table I) led to the conclusion that although there is a slight bathochromic shift with the spectra of **12a** compared to that of **11** the structures of **10** and **13a** cannot be defined as either of these extremes. The NMR spectra of several 5-*N*-alkyl derivatives in dimethyl sulfoxide showed an exchangeable hydrogen coupled to a hydrogen or hydrogens on an adjacent carbon, indicative of the amine structure. Furthermore, a decoupling experiment on the 5-*N*-isopropyl derivative **15** (structure in Table II) clearly showed a collapse of the doublet signal ascribed to the proton on nitrogen at δ 8.0 to a singlet when the proton

Table I[a]



10 **11** **12a** **13a**

	10	11	12a	13a
neutral	230 (29430)	228 (29410)		231 (30530)
	241 (sh, 31260)	242 (35320)		242 (sh, 35900)
		253 (35900)		
	259 (41000)	262 (37730)	265 (47430)	258 (44930)
	330 (4720)	327 (5330)	331 (3950)	325 (4480)
				332 (4450)
acidic	218 (23800)	219 (22240)	225 (20320)	220 (26640)
	259 (38240)	258 (36400)	263 (45510)	258 (42370)
		305 (sh, 11980)		
	319 (sh, 7060)	319 (8390)	327 (sh, 5350)	317 (sh, 6390)
basic	230 (sh, 39880)	239 (sh, 43350)		231 (39320)
	241 (sh, 34900)	253 (38000)		242 (39190)
	259 (41500)	262 (39740)	264 (47750)	258 (45830)
	330 (4800)	326 (5530)	330 (3980)	324 (4830)

[a] Ultraviolet spectra taken in methanol (neutral), acidified with hydrochloric acid or made basic with potassium hydroxide. Principal peaks (λ) and shoulders are indicated with the ϵ values in parentheses.

on the adjacent methinyl group at δ 4.5 was irradiated.[26] Methylation of **13a** with dimethylformamide dimethylacetal gave the 5-dimethylamine **12a** and not 2-(2-furyl)-5,6-dihydro-6-methyl-5-(methylimino)[1,2,4]triazolo-[1,5-*c*]quinazoline.[27] Similar treatment of **2** in acetonitrile yielded only the (dimethylamino)methinyl derivative of **2a**, as expected for an amine. When the imine is locked in place as in **11**, the corresponding 5-oxo compound was obtained on treatment with dilute acid (Experimental Section) whereas compounds without a substitute at position 6 are more stable to aqueous acid, an indication of the stabilizing influence of the aminoid form and/or the tautomeric equilibrium factor. Therefore, in order to supply one name and one canonical form for **2**, we favor the amine structure **2a** in this publication.[28]

Biological Test Results. The activities of **2** and selected analogues were assessed in the test systems men-

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(25) We are indebted to Drs. Karl Gelotte and Harold Meckler of the Technical Operations Department in the Chemical Operations Unit of CIBA-GEIGY for this procedure.
(26) We are indebted to Dr. Nina Gonnella of Drug Discovery Support, CIBA-GEIGY, for performing the decoupling experiment on a Bruker AM 300 instrument.
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(28) After the initial submission of the manuscript, an X-ray crystallographic analysis of a sample of **2** recrystallized from acetone confirmed the structure as **2a** with the oxygen of the furan nearer N-3 than N-1. (Dr. F. H. Clarke, CIBA-GEIGY, private communication).
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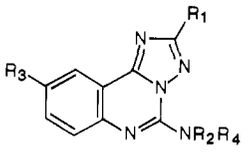
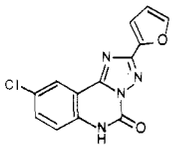
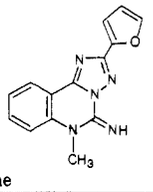
Table II. IC_{50} (Nanomolar) Values ± SEM



no.	R_1	R_2	R_3	R_4	salt	synthetic method (yield)[a]	mp, °C	binding IC_{50}, nM A_1	binding IC_{50}, nM A_2	ratio A_2/A_1	guinea pig cerebral cortex IC_{50}	guinea pig trachea IC_{50}
2		H	Cl	H	$MeSO_3H$	1A (56) 1B (61) 1C (53) 2A (24) 2B (71)	279–281	21 ± 3	3.3 ± 1.7	0.16	20	3
10		H	H	H		1A (64)	282–285	38 ± 24	27 ± 15	0.71	40	100
12b		CH_3	Cl	CH_3		1A (62)	195–198	>10000	>10000		>1000	>1000
13b		CH_3	Cl	H		1C (42)	166–168	89 ± 6	61 ± 3	0.69		>1000
14		CH_2CH_2OH	Cl	H		1B (66)	214–217	21 ± 4	56 ± 11	2.7		>1000
15		$CH(CH_3)_2$	Cl	H		1A (63) 1B (69)	140–141	22 ± 4	179 ± 64	8.2	400	>1000
16		$CH(CH_3)CH_2CH_3$	Cl	H	$MeSO_3H$	1A (80)	176–177	61 ± 13	158 ± 74	2.6		>1000
17		$C(CH_3)_3$	Cl	H		1B (34)	193–195	>10000	>10000			>1000
18		H	CH_3O	H		2B (29)	268–270	31 ± 5	19 ± 7	0.61		>10000
19		H	HO	H		2B (75)	359–360	9.5 ± 3.3	5.5 ± 3.0	0.58		1000 (relaxation at 10000)
20		H	$C_6H_5CH_2O$	H		2B (53)	274–276	145 ± 63	1290 ± 713	8.9		>10000
21		H	Cl	H	$MeSO_3H$	1A (84)	290–292	295 ± 107	145 ± 55	0.49	79	>1000
22		H	Cl	H		1B (43)	282–283	1570 ± 121	531 ± 324	0.34		>1000
23		H	Cl	H	$MeSO_3H$	2A (69)	247–252	324 ± 72	116 ± 34	0.36	200	>1000
24		H	Cl	H	$MeSO_3H$	2B (32)	290 dec	610 ± 93	1205 ± 449	2.0		>1000
25		H	Cl	H		1C (40)	203–206	827 ± 110	1580 ± 246	1.9	480	>1000
6							375–377	~10000	>10000			>1000
11					Me_3SO_3H	2A (26)	253–257	1219 ± 464	2914 ± 563	2.4	1483 ± 166	>1000
theophylline								>10000	>10000		10000[b]	3000 ± 100

[a] Yields are reported for the step leading to the free base in percent. [b] See ref 14.

tioned previously. The structures tested, synthetic method for the final step, and the IC_{50} values for the key compounds are summarized in Table II.

From the data it is obvious that **2** is the most potent A_2 antagonist in the four test systems and also the most A_2 selective. Replacement of the halogen by hydroxyl (structure **19**) gave a compound with binding comparable to **2** at both receptors, but in the tracheal model, inhibition of 2-chloroadenosine activity to the extent of 55% was observed at a 1 μM concentration, whereas 33% *relaxation* of the tissue occurred at a concentration of 10 μM. Replacement of chlorine by hydrogen (**10**) or methoxyl (**18**) reduced binding slightly, but only **10** showed activity in the other screens in the nanomolar range. Replacement of chlorine with the bulky benzyloxy group (**20**) caused a significant loss in binding activity, especially at the A_2 receptor. Replacement of the amino function by an alkylamino group caused a loss in activity and an increase in A_1 selectivity. Compounds **14** and **15** are as active in binding at the A_1 receptor as the lead compound **2** but are

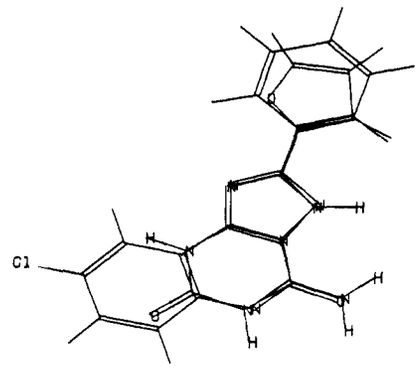


Figure 1. Comparison of energy-minimized configurations of **2a** and 8-phenylxanthine in which the furan ring of **2a** overlaps the 8-phenyl substituent.

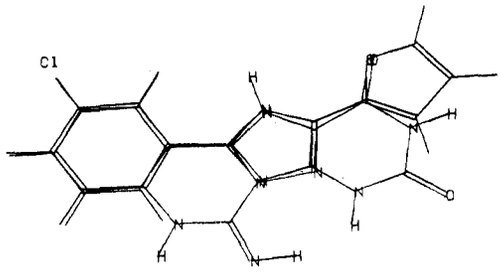


Figure 2. Comparison of **2b** with 8-phenylxanthine in which the benzene ring of **2b** overlaps the 8-phenyl substituent.

inactive in the nanomolar range in the tracheal model. Replacement of hydrogen on the exocyclic nitrogen by the bulky *tert*-butyl group (**17**) caused complete loss of activity. Replacement of hydrogen at N-6 by a methyl group resulted in a 30- to 100-fold loss of binding (**11** vs **10**), but the dimethylamino compound **12b**, lacking the exocyclic double bond, had no binding activity. The exocyclic double bond alone is insufficient for activity, as the carbonyl compound **6** was inactive. Modification of the 2-furyl group (compounds **21–25**) resulted in a severe loss in activity. The tetrahydro compound showed no antagonism in the trachea, but at 1 μM, it produced 22% intrinsic activity. In summary, with few exceptions, variation of structure **2** resulted in a significant loss of adenosine antagonist activity. Results from binding correlate rather well with those from the cerebral cortex model whereas lack of potency in the nanomolar range for most of the analogues in the tracheal model may be due to differences between central and peripheral tissues.

Modeling Studies. Molecular modeling studies show that **2a** or **2b** overlap significant portions of 8-arylxanthines, an indication that binding may occur at the same receptor site. Energy minimization indicates that **2** is nearly a flat molecule, and the configuration in which the oxygen of the furan ring is near N-1 has essentially the same energy as that where the oxygen is nearer N-3. Figure 1 illustrates the overlap of the furyl moiety of **2a** with the phenyl group of 8-phenylxanthine and the coincidence of the triazolopyrimidine portion with the imidazopyrimidine of the xanthine. In this configuration, three nitrogen atoms overlap, and the 5-amino group of **3** overlaps the carbonyl oxygen at position 4 in the xanthine. Since the 2-furyl moiety plays such a significant role in the binding of our compounds, the overlap illustrated in Figure 2 appears an attractive possibility. In this conformation, the benzene ring in our structure overlaps the 8-phenyl group of the xanthine, the triazole of our structure overlaps the imidazole of the xanthine (including both nitrogens), and a significant portion of the furan moiety overlaps part

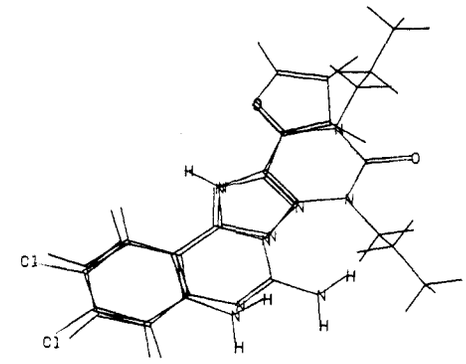


Figure 3. Comparison of **2a** with PACPX in which the benzene rings overlap. The furan ring is shown with the oxygen atom nearer N-1 than N-3.

of the pyrimidinedione moiety of the xanthine, including the overlap of oxygen atoms. If one compares the highly potent PACPX[9,33] with **2a** in the same manner (Figure 3), there is an additional overlap of the 2′-amino group of PACPX with the nitrogen at position 6 in our structure, which suggests another possible point of attachment to the receptor site.

In conclusion, **2** is a novel adenosine antagonist with a high affinity and moderate selectivity for the A_2 receptor and will provide a useful biological tool for the characterization of the effects of adenosine in its many actions on mammalian tissues.

Biochemical Test Procedures. A. [^{3}H]Cyclohexyladenosine (CHA) Binding (Adenosine A_1 Receptor). Binding of [^{3}H]CHA to adenosine A_1 receptors was measured in rat brain membranes.[29] Compound **2** and its analogues were tested as described previously.[18]

B. [^{3}H]-5′-*N*-[(Ethylcarbonyl)amino]adenosine (NECA) Binding (Adenosine A_2 Receptor). Binding of [^{3}H]NECA to adenosine A_2 receptors was measured in rat striatum.[30] Compounds were tested as described previously.[18] IC_{50} values were derived from specific binding data by using log–ligit transformation.[31]

C. In Vitro Inhibition of Adenosine Activation of Adenylate Cyclase. Compounds were tested for inhibition of adenylate cyclase activity of synaptoneurosomes (previously referred to as vesicles) prepared from guinea pig cerebral cortex and stimulated by 5 μM adenosine as previously described.[32]

D. Inhibition of 2-Chloroadenosine-Induced Relaxation in Histamine-Contracted Guinea Pig Trachea. The methodology used for testing **2** described previously[19] was applied to the analogues.

Experimental Section

All new compounds had satisfactory C, H, and N analyses and exhibited IR and NMR spectra consistent with the structures. Proton NMR were determined on a Varian EM-390 instrument in DMSO-d_6 solution with tetramethylsilane as internal standard. IR spectra taken in Nujol mulls were recorded on a Perkin-Elmer Model 457 spectrometer. UV spectra were determined on a Perkin-Elmer Lambda 7 UV–vis spectrophotometer. 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 5985 mass spectrometer.

Molecular Modeling. Figures 1–3 were generated with a Macro Model Molecular Modeling Package (34) running on a VAX 8600. The figures represent energy-minimized structures.

(33) Snyder, S. H.; Daly, J. W.; Bruns, R. F. Brit. Pat. 2,135,311A, August 30, 1984, to Johns Hopkins University.
(34) Version 1.1, available from Prof. W. Clark Still, Columbia University, New York, NY 10027.

9-Chloro-2-(2-furyl)[1,2,4]triazolo[1,5-*c*]quinazolin-5-(6*H*)-one (6). (a) To a solution of 2-furanamidine hydrochloride hydrate (20.0 g, 0.12 mol) in absolute ethanol (350 mL) was added sodium methylate (7.37 g, 0.136 mol) dissolved in absolute ethanol (250 mL). After the mixture was stirred for 5 min under nitrogen, it was filtered, and the filtrate was added to a solution of 2-amino-5-chlorobenzhydrazide (25.2 g, 0.148 mol) in chlorobenzene (500 mL) and absolute ethanol (300 mL) at 70 °C in an apparatus containing a water separator. The temperature was raised to 110 °C (outside temperature) over 1 h and then to 130 °C. After distillation ceased, the separator was removed, and a compensating addition funnel containing 4-Å molecular sieves was inserted between flask and condenser. Chlorobenzene (250 mL) was added, and the mixture was heated at reflux overnight under nitrogen. The hot mixture was filtered, and the filtrate was refrigerated to produce pale yellow crystals (14.5 g, 41%) of 5-(2-amino-5-chlorophenyl)-3-(2-furyl)-1*H*-1,2,4-triazole (**7**), mp 246–248 °C.

To a suspension of the triazole (2.5 g, 9.6 mmol) in dioxane (80 mL) was added trichloromethyl chloroformate (1.9 g, 9.6 mmol), and the mixture was stirred overnight under nitrogen. Triethylamine (0.97 g) was added, stirring was continued over 2 h, and the mixture was filtered. The off-white solid (2.4 g, 87%) was washed with water and then ether and recrystallized from dimethylacetamide/water to afford pure **6**: mp 375–377 °C; IR 1758 cm^{-1} (C=O); NMR δ 6.7 (m, 4′-*H*), 7.3 (m, 3′-*H*), 7.4–8.2 (m, 4 H), 12.5 (N*H*, exchangeable with D_2O).

(b) A mixture of 4-chloro-2-cyanophenyl isocyanate (**4b**) (8.0 g, 0.045 mol), 2-furoic acid hydrazide (6.3 g, .05 mol), and dioxane (250 mL) was stirred at reflux under nitrogen for 1 h and cooled, and the precipitate was collected, triturated with methanol, and air dried. This material (5.8 g) had not cyclized completely as indicated by a small nitrile peak in the IR spectrum (2220 cm^{-1}, Nujol), carbonyl peaks at 1640, 1660, and 1720 cm^{-1}, and the lack of carbonyl at 1758 cm^{-1}. The solid was suspended in a mixture of triethylamine (40 mL), absolute ethanol (350 mL), and methanesulfonic acid (1.3 mL) and stirred at reflux for 2 h. The material dissolved on warming but within 0.5 h a solid began to form. The mixture was cooled, and the solid was collected, washed with ethanol, and oven dried to afford 4.3 g (33%) of **6**, identical with that from the triazole **7** as indicated by TLC, IR and NMR comparison.

Under the same conditions, (tetrahydro-2-furoyl)hydrazine was converted to 9-chloro-2-(tetrahydro-2-furyl)[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one in 86% yield. It was recrystallized from ethanol to analytical purity, mp 241–243 °C.

Preparation of Triazole 7 from 6. A mixture of **6** (2.87 g, 10 mmol), 4 N aqueous sodium hydroxide (60 mL), and 2-methoxyethanol (60 mL) was stirred as reflux under nitrogen for 48 h. On cooling, a first crop of material was obtained. The filtrate was concentrated at reduced pressure to dryness, suspended in water (100 mL), and extracted with 3:1 ethyl acetate/tetrahydrofuran (5 × 75 mL). The extract was dried (Na_2SO_4), concentrated to dryness at reduced pressure, and triturated with water to afford a second crop of material. Refrigeration of the aqueous filtrate produced a third crop, and the combined material (2.2 g, 84%, mp 246–249 °C) showed an IR spectrum identical with that of **7** obtained by the route described previously.

5,9-Dichloro-2-(2-furyl)[1,2,4]triazolo[1,5-*c*]quinazoline (9). To a mixture of **6** (2.9 g, 10 mmol), phosphoryl chloride (50 mL), and phosphorus pentachloride (0.6 g) was added cautiously pyridine (2 mL), and the mixture was stirred under nitrogen for 24 h at a bath temperature of 120 °C. It was concentrated to dryness at reduced pressure, and the residue was suspended in warm methylene chloride (400 mL) and filtered free of starting material. The filtrate was concentrated to dryness, and the residual solid was triturated with water and filtered. The light tan product (1.7 g, 56%, mp 222–225 °C) was analytically pure after overnight drying under reduced pressure: IR 1620, 1600 cm^{-1} (no C=O or NH).

Under the same conditions, 9-chloro-2-(tetrahydro-2-furyl)-[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one was converted to 5,9-dichloro-2-(tetrahydro-2-furyl)[1,2,4]triazolo[1,5-*c*]quinazoline, mp 150–152 °C, in 61% yield.

9-Chloro-2-(2-furyl)[1,2,4]triazolo[1,5-*c*]quinazoline-5-(6*H*)-thione (3). To a heterogeneous mixture of 5-chloroanthranilonitrile (40.6 g, 0.266 mol) in water (200 mL) was added dropwise under nitrogen with vigorous stirring thiophosgene (20.3 mL, 0.263 mol) in water (200 mL). The red color gradually disappeared, and a yellow solid formed. After 4 h, the product was collected, washed several times with cyclohexane, and dried over phosphorous pentoxide in a vacuum dessicator. The product, 4-chloro-2-cyanophenyl isothiocyanate (**4a**, 46.0 g, 89%) showed peaks in the IR spectrum at 2230 cm^{-1} (CN) and 2048 cm^{-1} (NCS) and was used without further purification. A mixture of the isothiocyanate **4a** (121 g, 0.62 mol), 2-furoic acid hydrazide (79 g, 0.63 mol), and 2-methoxyethanol (1 L) was treated with stirring with tri-*n*-propylamine (68 mL) in 2-methoxyethanol (1 L), and the mixture was brought gradually to reflux under nitrogen. During stirring and gentle reflux over 12 h, a thick yellow precipitate formed. It was allowed to cool to 40 °C, collected, washed thoroughly with methanol, and oven-dried (90 °C) under vacuum. The product **3** (107 g, 57%, mp 350–355 °C dec) was analytically pure. Concentration of the mother liquor at reduced pressure gave two crops of less pure material (35.4 g): IR 1615, 1635 cm^{-1}; NMR δ 6.8 (m, 4′-*H*), 7.35 (d, 3′-*H*), 7.6–8.2 (m, 4 H), 14.1 (s, N*H*, exchangeable with D_2O).

Reaction of **4a** with 5-bromo-2-furylcarbohydrazide produced the corresponding thiono compound in 60% yield: mp 273–276 °C; IR 1595, 1620, 1640 (weak) cm^{-1}; NMR δ 6.9 (m, 4′-*H*), 7.25 (d, 3′-*H*), 7.6–8.2 (m, 4 H), 14.2 (br s, N*H*); MS 380 (M^+), 301 ($^-$Br).

Reaction of **4a** with 3-furylcarbohydrazide produced the corresponding 2-(3-furyl)thione in 53% yield: mp >300 °C; IR 1620, 1590 cm^{-1}; NMR δ 6.9 (d, 4′-*H*), 7.3–8.0 (m, 4 H), 8.35 (m, 1 H), 13.7 (br s, 1 H).

Reaction of 2-isothiocyanatobenzonitrile (ROC/RIC Chemical Co.) with 2-furylcarbohydrazide gave 2-(2-furyl)[1,2,4]triazolo-[1,5-*c*]quinazoline-5(6*H*)-thione in 58% yield: mp >300 °C; IR 1630 cm^{-1}; NMR δ 6.8 (m, 4′-*H*), 7.3 (d, 3′-*H*), 7.4–8.3 (m, 5 H), 13.9 (br s, 1 H).

9-Chloro-2-(2-furyl)-5-thiocyanato[1,2,4]triazolo[1,5-*c*]-quinazoline (8b). To a stirring suspension of sodium hydride (50% in oil, 7.2 g, 0.15 mol) in dry tetrahydrofuran (700 mL) under nitrogen was added thiono compound **3** (45 g, 0.149 mol) in 5-g batches. It was stirred at ambient temperature for 2 h and became brick red. More solvent (600 mL) was added to aid stirring, and cyanogen bromide (15.9 g, 0.15 mol) in tetrahydrofuran (100 mL) was added dropwise over 15 min. The mixture thinned and turned canary yellow. After an additional 1 h of stirring, ice–water (1.3 L) was added with stirring, whereupon the mixture first cleared and then turned to a thick yellow mixture of solid and liquid. After 15 min it was filtered, and the precipitate was washed with cold water (3 × 300 mL), pressed dry on the filter, and then oven-dried (90 °C) at reduced pressure. The material was ground and redried to obtain **8b** (45.8 g, 93%, mp 211–212 °C) suitable for further work. For analysis, a sample was recrystallized from 2-methoxyethanol, mp 218–220 °C: IR 1610, 1590 cm^{-1}; NMR δ 6.75 (m, 4′-*H*), 7.32 (d, 3′-*H*), 7.9–8.2 (m, 3 H), 8.35–8.5 (m, 1 H); MS 327 (M^+), 269 ($^-$SCN). Similarly, the corresponding 5′-bromo compound was prepared in 81% yield: mp 290–295 °C dec; IR 1615, 1595 cm^{-1}; NMR δ 6.95 (d, 4′-*H*), 7.45 (d, 3′-*H*), 8.05–8.55 (m, 3 H).

9-Chloro-2-(2-furyl)-5-(methylthio)[1,2,4]triazolo[1,5-*c*]-quinazoline (8a). To a solution of sodium methoxide (2.12 g, 0.04 mol) in dry methanol (800 mL) was added the thiono compound **3** (11.3 g, 0.04 mol), and the mixture was stirred under nitrogen as the temperature was raised to 60 °C. Methyl iodide (2.5 mL, 0.04 mol) was added, whereupon the mixture changed from red to yellow. It was stirred under reflux for 2 h and cooled to 10 °C, and the solid was collected, washed with methanol and dried at reduced pressure to afford pure **8a** (10.6 g, 84%): mp 263–265 °C; IR 1590, 1615 cm^{-1}; NMR δ 2.7 (s, CH_3), 6.8 (m, 4′-*H*), 7.3 (d, 3′-*H*), 7.85–8.3 (m, 4 H).

In the same way, 9-chloro-2-(3-furyl)-5-(methylthio)[1,2,4]-triazolo[1,5-*c*]quinazoline was obtained in 80% yield: mp 187–190 °C; IR 1615, 1585 cm^{-1}; NMR δ 2.75 (CH_3S), 7.0 (d, 4′-*H*), 7.75–8.4 (m, 5 H); MS 316 (M^+). Also prepared was 2-(2-furyl)-5-(methylthio)[1,2,4]triazolo[1,5-*c*]quinazoline in 82% yield, mp 188–190 °C; IR 1620, 1595 cm^{-1}; NMR δ 2.9 (CH_3S), 6.8 (m, 4′-*H*), 7.35 (d, 3′-*H*), 7.6–8.5 (m, 5 H).

9-Chloro-2-(2-furyl)[1,2,4]triazolo[1,5-*c*]quinazolin-5-amine (2a). Method 1A. A mixture of **8a** (5.7 g, 19 mmol) and concentrated ammonium hydroxide presaturated with ammonia

at 0 °C (300 mL) was heated in a stainless steel pressure vessel at an outside temperature of 150 °C for 16 h, which produced an internal pressure of 250 psi. The mixture was cooled, and the product was collected by filtration, washed with cold water, and oven-dried at reduced pressure to afford **2a** as a pale yellow solid (2.9 g, 56%), mp 269–271 °C. It was treated with an equimolar amount of methanesulfonic acid in 2-methoxyethanol to give the methanesulfonate salt, mp 270–275 °C, after recrystallization from 2-methoxyethanol.

Partial evaporation of the ammoniacal mother liquor gave a second product (1.3 g, mp 248–250 °C), which was converted to the methanesulfonate salt, mp 268–269 °C. Analytical data confirmed the structure as the salt of **7**: IR 1560, 1575, 1630, ~2680 (br) cm^{-1}; NMR δ 2.55 (CH_3S), 6.85 (m, 4′-*H*), 7.1–7.5 (m, 3 H), 7.95–8.15 (m, 2 H), 9.1–9.7 (br s, 4 H); MS 260 (M^+ for free base); ^{13}C NMR δ 112.13 (C-4′), 112.30 (C-3′), 114.04 (C-10a), 122.09 (C-10), 126.78 (C-9), 126,86 (C-7), 132.15 (C-8), 143.74 (C-6a), 144.86 (C-2), 145.20 (C-2′ and C-5′), 150.78 (C-10b), 155.47 (C-5).[35]

Method 1B. A solution of **8b** (49.2 g, 158 mmol) in 1,3-dimethyl-2-imidazolidinone (750 mL) was treated with stirring with ammonia gas in an ice bath whereupon it gradually turned dark red. The internal temperature rose from 10 to 15 °C in the first 15 min but gradually fell over 1 h to 7 °C. Ammonia was added over 3 h. It was then treated with ice–water (1.8 L) with stirring, which caused an exotherm to 35 °C. It was cooled to 20 °C and filtered, and the yellow solid was washed with water until the washings were colorless. The precipitate was slurried in methanol (700 mL), refrigerated overnight, recollected, and pressed dry on the filter. The solid was taken up in warm (80 °C) dimethylacetamide (600 mL) and filtered, and the filtrate was treated with absolute ethanol (900 mL) with stirring and cooling. The bright yellow solid was collected, washed with cold ethanol (3 × 300 mL), and dried in a vacuum oven at 90–100 °C (12 mm) for 40 h to give pure **2a** (26 g, 61%): mp 278–279 °C; IR 3440, 1675, 1608, 1580, 1550, 1525, 1500 cm^{-1}; NMR δ 6.8–6.9 (m, 4′-*H*), 7.3 (d, 3′-*H*), 7.5–8.3 (m, 6 H, 4 H after D_2O exchange); UV (MeOH), (λ, ε) 233 (25 680), 243 (sh, 28 630), 259 (41 040), 331 (4590), 336–344 (4520, plateau); MS 285 (M^+).

Method 1C. A mixture of ammonium hydroxide saturated with ammonia at 0 °C (50 mL) and **9** (1.52 g, 50 mmol) was heated in a stainless steel pressure vessel at 150 °C for 6 h. The mixture was cooled, and the solid material was collected, washed with water, dried, and recrystallized from dimethylacetamide/ethanol to afford pure **2a** (0.76 g, 53%), mp 277–279 °C.

Method 2A. To a suspension of **7** (5.0 g, 19 mmol) in methanol (150 mL) at 60 °C was added cyanogen bromide (1.85 g, 17.5 mmol). This was stirred at reflux under nitrogen over 20 h, triethylamine was added (2.5 mL, 17 mmol), and reflux was continued for 1 h. It was cooled, and the solid was collected and recrystallized from ethyl acetate to afford **2** (1.2 g, 24%), mp 268–270 °C. It was suspended in methanol and treated with an equimolar amount of methanesulfonic acid, and the pure salt was precipitated by addition of ether, mp 279–281 °C.

In a similar way, 5-(2-amino-4-chlorophenyl)-3-(2-thienyl)-1*H*-1,2,4-triazole, mp 209–214 °C, was converted to **23** as free base, mp 264–268 °C, in 69% yield and thence to the methanesulfonate salt: mp 247–252 °C; IR 1710 cm^{-1}; NMR δ 2.7 (s, CH_3S), 7.3 (m, 1 H), 7.5–8.3 (m, 5 H), 9.0–11.0 (s, br, 3 H).

In addition, 3-(2-furyl)-5-[2-(methylamino)phenyl]-1*H*-1,2,4-triazole, mp 179–183 °C, was converted to **11** in 26% yield. Material that failed to dissolve during methanesulfonate salt formation was identified as 2-(2-furyl)-6-methyl[1,2,4]triazolo-[1,5-*c*]quinazolin-5(6*H*)-one, mp 238.5–241.5 °C (26% yield). Compound **11**: IR 1695, 1610 cm^{-1}; NMR δ 2.3 (CH_3S), 4.0 (CH_3N), 6.9 (m, 4′-*H*), 7.55 (d, 3′-*H*), 7.7–8.6 (m, 5 H), 10.4 (br s, 2 H). Oxo compound: IR 1710, 1650, 1615 cm^{-1}; NMR δ 3.8 (CH_3N), 6.7–6.8 (m, 4′-*H*), 7.3 (d, 3′-*H*), 7.4–8.4 (m, 5 H).

Method 2B.[25] To a slurry of **7** (15.1 g, 58 mmol) in 2-propanol (300 mL) was added 50% aqueous cyanamide (7.4 mL, 0.1 mol) followed by dilute sulfuric acid (3.7 g of concentrated acid dissolved in 4 mL of water). The mixture was heated to reflux for 6 h and cooled to room temperature, and the pH of solution was adjusted to 7 by addition of 2.5 mL of 10% aqueous sodium hydroxide. The mixture was cooled to 5 °C, and the product was collected, washed with cold ethanol (3 × 20 mL), and dried at 80 °C (12 mm) over 18 h. The tan solid (11.7 g, 71%), mp ~275 °C, was identical with that obtained from method 1B by IR/NMR/TLC comparison.

In a similar way, 5-(2-amino-4-methoxyphenyl)-3-(2-furyl)-1*H*-1,2,4-triazole, obtained as an oil, was converted to **18** in 29% yield: IR 3450, 3120, 1675, 1620, 1590 cm^{-1}; NMR δ 3.9 (s, CH_3O), 6.7 (m, 4′-*H*), 7.3 (d, 3′-*H*), 7.3–8.0 (m, 6 *H*, 2 exchangeable with D_2O). Also, 5-[2-amino-4-(benzyloxy)phenyl]-3-(2-furyl)-1*H*-1,2,4-triazole, mp 181–183 °C, was converted to **20** in 53% yield: IR 3450, 1680, 1620, 1595 cm^{-1}; NMR δ 5.3 (s, CH_2), 6.9 (m, 4′-*H*), 7.2–8.0 (11 H, 2 exchangeable with D_2O). Also, 5-(2-amino-4-hydroxyphenyl)-3-(2-furyl)-1*H*-1,2,4-triazole was converted to **19** in 75% yield: IR 3435, 1680, 1630, 1590 cm^{-1}; NMR δ 6.85 (m, 4′-*H*), 7.3–8.2 (m, 8 H, 1 exchangeable with D_2O), 10.0 (s, *H*O). In addition 5-(2-amino-4-chlorophenyl)-3-(2-pyrrolyl)-1*H*-1,2,4-triazole, mp 165–170 °C dec, was converted to **24** in 32% yield: IR 3260, ~2600 (br), 1715, 1610, 1565 cm^{-1}; NMR δ 2.5 (s, CH_3S), 6.1 (m, 4′-*H*), 6.9 (m, 5′-*H*), 7.0 (m, 3′-*H*), 7.6 (d, H at 7), 7.8 (dd, H at 8), 8.2 (d, H at 10), 9.0 (s, br, 3 H), 11.9 (s, 1′-*H*).

5-(Dimethylamino)-2-(2-furyl)[1,2,4]triazolo[1,5-*c*]quinazoline (12a). (a) A mixture of 40% aqueous dimethylamine saturated with dimethylamine gas at 10 °C (300 mL) and 2-(2-furyl)-5-(methylthio)[1,2,4]triazolo[1,5-*c*]quinazoline (5.08 g) was heated in a stainless steel pressure reactor at an external temperature of 150 °C overnight. The internal pressure fluctuated between 150 and 175 psi. The mixture was ice-cooled and evaporated at reduced pressure to remove much of the dimethylamine. It was diluted with water (100 mL), and the solid was collected and recrystallized from ethanol/water to afford the pure product (3.2 g, 64%): mp 123–125 °C; IR 1630, 1610, 1560, 1530 cm^{-1}; NMR δ 3.45 (2 CH_3), 6.8 (m, 4′-*H*), 7.35 (m, 3′-*H*), 7.4–8.35 (m, 5 H); MS 279.

(b) A mixture of 2-(2-furyl)-5-(methylamino)[1,2,4]triazolo-[1,5-*c*]quinazoline, mp 193–195 °C, prepared from the corresponding thiono compound via method 1A, (265 mg, 1 mmol), dimethylformamide (5 mL), and dimethylformamide dimethyl acetal (0.5 mL) was stirred under nitrogen at 140 °C over 15 h. It was cooled and treated dropwise with stirring with methanol (5 mL) and water (30 mL), and the precipitate was washed with water, taken up in ether, and filtered. The filtrate was concentrated to dryness at reduced pressure, taken up in toluene, reconcentrated to a pale yellow oil, and then crystallized from 2-propanol to afford the same material as obtained by the previous route, as shown by IR/NMR/TLC comparison. The yield was 110 mg (40%). TLC indicated starting material as the only impurity in the mother liquors.

9-Chloro-5-[[(dimethylamino)methinyl]imino]-2-(2-furyl)[1,2,4]triazolo[1,5-*c*]quinazoline. To a suspension of **2** (285 mg, 1 mmol) in acetonitrile (23 mL) under stirring was added dimethylformamide dimethyl acetal (0.7 mL), and the mixture was heated at reflux for 3 h under nitrogen. The dark red solution was concentrated to dryness at reduced pressure, and the residual solid was triturated with ether, collected, and dried at 80 °C (0.1 mm) for 16 h. The product, mp 217–220 °C, (0.32 g, 94%) was analytically pure: IR 1638, 1621, 1583, 1548, 1499 cm^{-1}; NMR δ 3.1 (d, 2 CH_3N), 6.7 (m, 4′-*H*), 7.25 (m, 3′-*H*), 7.7 (m, 2 H, at 7- and 8-positions), 7.9 (d, 5′-*H*), 8.2 (d, H at 10), 8.85 (s, C*H*=); MS 341 (M^+), 326 ($^-CH_3$).

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(35) The analysis of the ^{13}C NMR spectrum of **2**, run on a Bruker AM-300 instrument with TMS as internal standard, was done by Karl Gunderson.