73799-54-9; 18·HCl, 73799-56-1; 19·HCl, 73799-62-9; 20·HCl, 73799-60-7; 21·HCl, 73799-58-3; 22·HCl, 73799-51-6; *N*-(1,3,4,6,7,11bα-hexahydro-2*H*-benzo[*a*]quinolizin-2β-yl)formamide, 82059-25-4; *N*-(1,3,4,6,7,11bα-hexahydro-2*H*-benzo[*a*]quinolizin-2β-yl)methylamine, 75054-28-3; methanesulfonyl chloride, 124-63-0; sulfamide, 7803-58-9; 9,10-dimethoxy-1,3,4,6,7,11bα-hexahydro-2*H*-benzo[*a*]quinolizin-2β-ylamine, 73799-49-2; 10-chloro-1,3,4,6,7,11bα-hexahydro-2*H*-benzo[*a*]quinolizin-2β-ylamine, 84051-77-4; *N*-(1,3,4,6,7,11bα-hexahydro-2*H*-benzo[*a*]quinolizin-2β-yl)methylamine dihydrochloride, 84051-78-5.

(*E*)-3-(4-Oxo-4*H*-quinazolin-3-yl)-2-propenoic Acids, a New Series of Antiallergy Agents

Ronald A. LeMahieu,*[†] Mathew Carson,[†] William C. Nason,[†] David R. Parrish,[†] Ann F. Welton,[‡] Herman W. Baruth,[‡] and Bohdan Yaremko[‡]

Chemical Research Department and Department of Pharmacology, Hoffmann-La Roche Inc., Nutley, New Jersey 07110.
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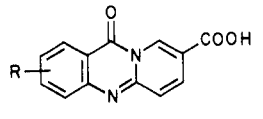
A series of substituted (*E*)-3-(4-oxo-4*H*-quinazolin-3-yl)-2-propenoic acids was prepared and evaluated in the rat passive cutaneous anaphylaxis (PCA) test for antiallergic activity. Alkoxy, alkylthio, and isopropyl substituents at the 6- or 8-positions provided highly potent compounds. Conversion to the *Z* isomer, reduction of the side chain double bond, or reduction of the quinazoline ring resulted in substantial loss of activity. Among the analogues that exhibited oral activity in the PCA test, (*E*)-3-[6-(methylthio)-4-oxo-4*H*-quinazolin-3-yl]-2-propenoic acid (**5i**) was the most potent.

Disodium cromoglycate (DSCG) is the only antiallergy drug currently available for the prophylactic treatment of bronchial asthma believed to act by inhibiting the release of mediators of allergic reactions from sensitized mast cells. Since the introduction of DSCG, which is not orally active, numerous compounds that have similar pharmacological properties but are orally active in animal models have been described in the scientific literature.[1]

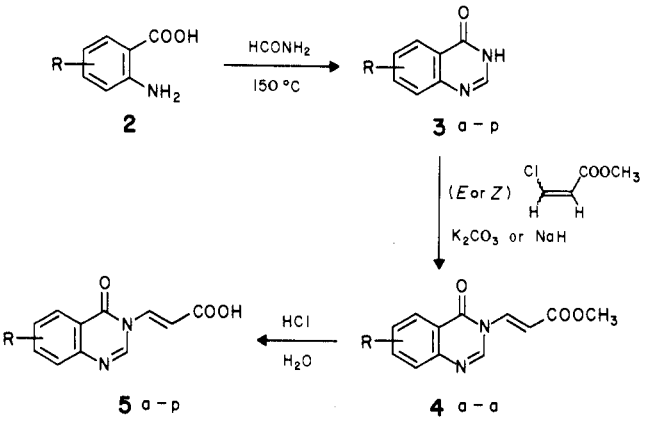
Several recent publications,[2,3] have disclosed the antiallergic activity of substituted pyrido[2,1-*b*]-quinazolinecarboxylic acids (**1**). We describe here a new series of potential antiallergy agents, the (*E*)-3-(4-oxo-4*H*-quinazolin-3-yl)-2-propenoic acids (**5**), which can be considered bicyclic analogues of **1**.



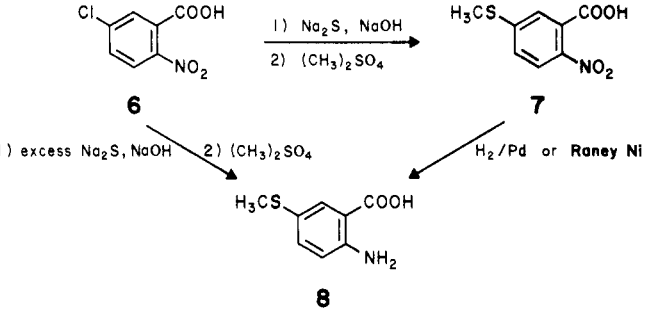
1, R = 2-OCH_3, 2-$CH(CH_3)_2$

Chemistry. The (*E*)-3-(4-oxo-4*H*-quinazolin-3-yl)-2-propenoic acids (**5**) were prepared as shown in Scheme I. The crucial intermediates required were the quinazolin-4(3*H*)-ones (**3**) and the methyl ester of 3-chloro-2-propenoic acid. The substituted anthranilic acids (**2**) needed for the preparation of the quinazolin-4(3*H*)-ones were prepared either by literature procedures or as described under Experimental Section. Special attention was given to development of an efficient procedure for the synthesis of 2-amino-5-(methylthio)benzoic acid (**8**), which is the intermediate needed for the preparation of the most potent analogue (**5i**). Initially, **8** was prepared (Scheme II) by catalytic hydrogenation of **7**, which required several catalyst loadings. During the course of this work we examined the reported[4] reaction of **6** with 1 equiv of sodium sulfide in base, followed by methylation with dimethyl sulfate to give **7**. In the presence of excess sodium sulfide, a facile reduction also occurred, providing an extremely efficient conversion of **6** directly to **8**. Heating the anthranilic acids (**2**) with formamide[5] gave the quinazolin-4(3*H*)-ones (**3**, Table I).

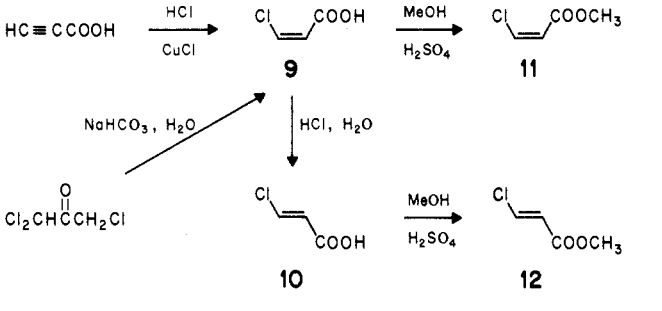
Scheme I



Scheme II



Scheme III



Two different literature methods were used to prepare the required 3-chloro-2-propenoic acids (Scheme III).

[†] Chemical Research Department.
[‡] Department of Pharmacology.

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Table I. Quinazolin-4(3*H*)-ones (3)

no.	R	formula	mp, °C	yield, %	recrystn solvent	anal.
3a	H	$C_8H_6N_2O$[a]	215	65	EtOH	
3b	6-OCH_3	$C_9H_8N_2O_2$[b]	238-240	90	CH_2Cl_2-MeOH	
3c	8-OCH_3	$C_9H_8N_2O_2$[c]	298-300	49	MeOH	
3d	6-$OCH(CH_3)_2$	$C_{11}H_{12}N_2O_2$	206-208	83	MeOH	C, H, N
3e	6-OH	$C_8H_6N_2O_2$[d]	>300	80	DMF-H_2O	
3f	6-$O(CH_2)_2OH$	$C_{10}H_{10}N_2O_3$	200-202	68	MeOH	C, H, N
3g	6-$O(CH_2)_2N(C_2H_5)_2$·HCl	$C_{14}H_{19}N_3O_2$·HCl	233-234	47	2-PrOH-H_2O	C, H, N, Cl^-
3h	6-Cl	$C_8H_5ClN_2O$[b]	265-267	68	MeOH-EtOAc	
3i	6-SCH_3	$C_9H_8N_2OS$	203-204.5	92	MeOH	C, H, N, S
3j	6-$SCH(CH_3)_2$	$C_{11}H_{12}N_2OS$	141-143	77	CH_2Cl_2-MeOH	C, H, N, S
3k	6-$CH(CH_3)_2$	$C_{11}H_{12}N_2O$	152-153	87	CH_2Cl_2-hexane	C, H, N
3l	6-Δ	$C_{11}H_{10}N_2O$	201-202	75	MeOH-EtOAc	C, H, N
3m	6,7-$(OCH_3)_2$	$C_{10}H_{10}N_2O_3$	296-297	93	not recrystd	C, H, N
3n	6,8-$(OCH_3)_2$	$C_{10}H_{10}N_2O_3$	280-282	37	MeOH	C, H, N
3o	6,8-$(CH_3)_2$	$C_{10}H_{10}N_2O$[b]	244-247	56	MeOH	
3p	6,8-$[CH(CH_3)_2]_2$	$C_{14}H_{18}N_2O$	164-165	49	CH_2Cl_2-hexane	C, H, N

[a] W. L. F. Armarego, *J. Appl. Chem.*, 11, 70 (1961). [b] B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy, and J. H. Williams, *J. Org. Chem.*, 17, 141 (1952). [c] R. N. Iyer, N. Anand, and M. L. Dhar, *J. Sci. Ind. Res.*, 15C, 1 (1956). [d] J. Maillard, M. Benard, M. Vincent, Vo-Van-Tri, R. Jolly, R. Morin, M. Benharkate, and C. Menillet, *Chim. Ther.*, 231 (1967).

Table II. Methyl (*E*)-3-(4-Oxo-4*H*-quinazolin-3-yl)-2-propenoates (4)

no.	R	formula	mp, °C	yield, %	recrystn solvent	anal.
4a	H	$C_{12}H_{10}N_2O_3$	173-174.5	63	CH_2Cl_2-Et_2O	C, H, N
4b	6-OCH_3	$C_{13}H_{12}N_2O_4$	184-186	85	CH_2Cl_2-MeOH	C, H, N
4c	8-OCH_3	$C_{13}H_{12}N_2O_4$	203-208	57	$CHCl_3$-MeOH	C, H, N
4d	6-$OCH(CH_3)_2$	$C_{15}H_{16}N_2O_4$	156-157	86	CH_2Cl_2-MeOH	C, H, N
4e	6-OH	$C_{12}H_{10}N_2O_4$	255-258	84	EtOAc-MeOH	C, H, N
4f	6-$O(CH_2)_2N(C_2H_5)_2$	$C_{18}H_{23}N_3O_4$	131-133	89	not recrystd	C, H, N
4g	6-Cl	$C_{12}H_9ClN_2O_3$	171-172	53	CH_2Cl_2-MeOH	C, H, N, Cl
4h	6-SCH_3	$C_{13}H_{12}N_2O_3S$	169-170	90	CH_2Cl_2-MeOH	C, H, N, S
4i	6-$SCH(CH_3)_2$	$C_{15}H_{16}N_2O_3S$	129-131	82	MeOH	C, H, N, S
4j	6-$CH(CH_3)_2$	$C_{15}H_{16}N_2O_3$	142-143	81	MeOH	C, H, N
4k	6-Δ	$C_{15}H_{14}N_2O_3$	177-178	61	CH_2Cl_2-MeOH	C, H, N
4l	6,7-$(OCH_3)_2$	$C_{14}H_{14}N_2O_5$	242-243	53	CH_2Cl_2-MeOH	C, H, N
4m	6,8-$(OCH_3)_2$	$C_{14}H_{14}N_2O_5$	224-226	79	$CHCl_3$-MeOH	C, H, N
4n	6,8-$(CH_3)_2$	$C_{14}H_{14}N_2O_3$	139-141	80	$CHCl_3$-MeOH	C, H, N
4o	6,8-$[CH(CH_3)_2]_2$	$C_{18}H_{22}N_2O_3$	102-103	82	MeOH	C, H, N

Addition of hydrochloric acid to propiolic acid, catalyzed by cuprous chloride,[6] provided the *Z*-isomer **9** in 94% yield. The Favorskii reaction of 1,1,3-trichloroacetone[7] gave **9** in 63% yield. Isomerization of **9** with aqueous hydrochloric acid[6] gave the *E*-isomer **10**. Both **9** and **10** were converted in high yield to the corresponding methyl esters **11** and **12** as described.[6]

Quinazolin-4(3*H*)-ones **3** are known to alkylate on the nitrogen in the 3-position.[8] Initially, the alkylation of the quinazolin-4(3*H*)-ones was carried out by conversion to the sodium salts with sodium hydride in dimethylformamide, followed by treatment with (*E*)-methyl ester **12** to yield the esters **4**. Most of the compounds in Table II were prepared by this procedure. It was discovered later that this step could be conducted more conveniently by using potassium carbonate as the base and the more accessible (*Z*)-methyl ester **11** in refluxing acetone. Both procedures are described under Experimental Section for **5i**. In the cases where the R substituent in **3** was hydroxy, prior protection as the trimethylsilyl ether was required for smooth conversion to **4**.

The stereochemistry of the esters **4** was assigned based on the coupling constants for the olefinic protons (J = 14.5–15 Hz) in the NMR spectra. Apparently, the intermediate in the reaction process loses its stereochemical integrity by rotation before loss of chloride ion, since both the (*E*)- and (*Z*)-chloro esters yield **4** only as the thermodynamically more stable *E* isomer. There is ample literature precedent for this process. An addition–elimination mechanism has been proposed for the reaction of nucleophiles with β-chloroacrylonitrile.[9] In this case, both the *E* and *Z* isomers gave only the *E* product when reacted with piperidine. In another example, nucleophilic attack of ethoxide ion on (*E*)- or (*Z*)-3-chlorocrotonates yielded exclusively the *E* product.[10]

Since the esters **4** were unstable to aqueous base, hydrolysis to the acids **5** was accomplished with refluxing 6 N hydrochloric acid, from which the products usually separated in pure form. In larger scale hydrolyses, 1-octanol was used to retard foaming. The acids (**5**, Table III) also were obtained as only the *E* isomers, established again by the coupling constants for the olefinic protons (J = 15 Hz) in the NMR spectra.

(1) J. W. F. Wasley in "Medicinal Chemistry Advances", F. G. De Las Heras and S. Vega, Eds., Pergamon Press, Oxford, England, 1981, pp 329–343.
(2) C. F. Schwender, B. R. Sunday, D. J. Herzig, E. K. Kusner, P. R. Schumann, and D. L. Gawlak, *J. Med. Chem.*, **22**, 748 (1979).
(3) J. W. Tilley, R. A. LeMahieu, M. Carson, R. W. Kierstead, H. W. Baruth, and B. Yaremko, *J. Med. Chem.*, **23**, 92 (1980).
(4) J. C. Sircar, T. Capiris, and S. J. Kresten, *J. Heterocycl. Chem.*, 18, 117 (1981).
(5) W. L. F. Armarego, "Fused Pyrimidines", Part I, Interscience, New York, NY, 1967, pp 74–75.
(6) A. N. Kurtz, W. E. Billups, R. B. Greenlee, H. F. Hamil, and W. T. Pace, *J. Org. Chem.*, **30**, 3141 (1965).
(7) C. Rappe, *Acta Chem. Scand.*, **19**, 31 (1965).
(8) W. L. F. Armarego, ref 5, pp 104–106.
(9) F. Scotti and E. J. Frazza, *J. Org. Chem.*, **29**, 1800 (1964).
(10) D. E. Jones, R. O. Morris, C. A. Vernon, and R. F. M. White, *J. Chem. Soc.*, 2349 (1960).

Table III. (*E*)-3-(4-Oxo-4*H*-quinazolin-3-yl)-2-propenoic Acids (5)

no.	R	formula	mp, °C	yield, %	anal.	rat PCA test[a] % inhibn[b] 16 mg/kg ip	32 mg/kg po	ID_{50},[c] mg/kg po
5a	H	$C_{11}H_8N_2O_3$	250–254	62	C, H, N		55	>10
5b	6-OCH_3	$C_{12}H_{10}N_2O_4$	298–299	71	C, H, N	49	23	
5c	8-OCH_3	$C_{12}H_{10}N_2O_4$	289–291	54	C, H, N	82	45[d]	
5d	6-$OCH(CH_3)_2$	$C_{14}H_{14}N_2O_4$	232–233	27	C, H, N	87	70	0.9 (0.35–7.2)
5e	6-OH	$C_{11}H_8N_2O_4$	294–296	81	C, H, N	56		
5f	6-$O(CH_2)_2OH$	$C_{13}H_{12}N_2O_5$	247–248	35	C, H, N	67 ($p < 0.005$)	80	>10
5g	6-$O(CH_2)_2N(C_2H_5)_2 \cdot HCl$	$C_{17}H_{21}N_3O_4 \cdot HCl$	227–230	57	C, H, N, Cl^-	16 ($p < 0.4$)	inactive	
5h	6-Cl	$C_{11}H_7ClN_2O_3$	297–298	69	C, H, N, Cl	79	49 ($p < 0.005$)	
5i	6-SCH_3	$C_{12}H_{10}N_2O_3S$	272–274	81	C, H, N, S	87	75	0.6 (0.3–1.5)
5j	6-$SCH(CH_3)_2$	$C_{14}H_{14}N_2O_3S$	238–239	59	C, H, N, S	59	56	
5k	6-$CH(CH_3)_2$	$C_{14}H_{14}N_2O_3$	244–245	78	C, H, N	100	89	1.4 (0.8–2.9)
5l	6-Δ	$C_{14}H_{12}N_2O_3$	291–293	34	C, H, N	100	81[d]	>10
5m	6,7-$(OCH_3)_2$	$C_{13}H_{12}N_2O_5$	303–305	85	C, H, N	88		
5n	6,8-$(OCH_3)_2$	$C_{13}H_{12}N_2O_5$	305–307	67	C, H, N	81	31[e]	
5o	6,8-$(CH_3)_2$	$C_{13}H_{12}N_2O_3$	284–288	88	C, H, N	82	70	9.1 (3.6–34.5)
5p	6,8-[CH(CH$_3$)]	$C_{17}H_{20}N_2O_3$	181–182	55	C, H, N	70	91	1.3 (0.8–2.2)
disodium cromoglycate						46 (8 mg/kg)	18	

[a] As described in ref 2 with a 5-min pretreatment time. [b] $p < 0.001$ using Student's *t* test, except as noted in parentheses. [c] Numbers in parentheses represent Fieller's 95% confidence limits. [d] 10-min pretreatment time. [e] 30-min pretreatment time.

Scheme IV

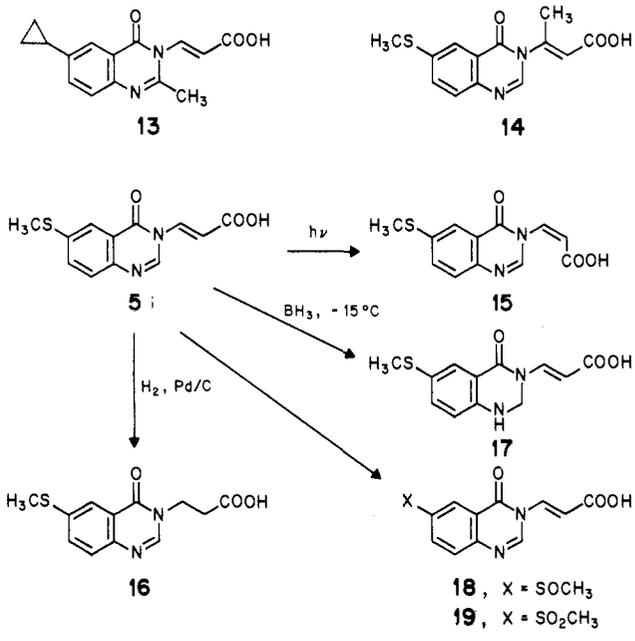


Table IV. Rat Passive Cutaneous Anaphylaxis Test

no.[a]	% inhibn, 16 mg/kg ip
4d	46
4h	39
13	39 ($p < 0.01$)
14	9 ($p < 0.05$)
15	11 ($p < 0.05$)
16	14 ($p < 0.01$)
17	53 ($p < 0.01$)
18	89 (48% at 32 mg/kg po)
19	70

[a] All compounds are described under Experimental Section.

Structural modifications of some of the more active compounds were made in order to determine requirements for high activity. The 2-methylquinazoline analogue **13** and the 3-methylpropenoic acid derivative **14** (Scheme IV) were prepared as in Scheme I. The *E* stereochemistry of **14** was assigned based on the NMR spectrum in which the chemical shift of the 3-methyl substituent was δ 2.46. Photoisomerization of **14** in Me_2SO gave a 2:1 (*Z*/*E*) mixture in which the new 3-methyl resonance appeared at δ 2.25. The observed upfield shift of the 3-methyl substituent in the *Z* isomer of **14** was expected based on the work of Jackman and Wiley,[11] who found that an allylic methyl trans to an alkoxycarbonyl group resonated at higher field than did the corresponding *cis*-methyl.

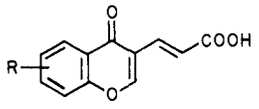
Photoisomerization of **5** gave a 4:1 (*Z*/*E*) mixture from which pure **15** was separated by HPLC. Hydrogenation of **5** gave the propionic acid **16** and reduction with diborane at −15 °C gave **17**. Oxidation of **5** with sodium periodate gave the sulfoxide **18**, while oxidation with hydrogen peroxide in acetic acid gave the sulfone **19** (Scheme IV).

Structure–Activity Relationships. The compounds described were evaluated for antiallergy activity in the rat passive cutaneous anaphylaxis (PCA) test, and the results are reported in Tables III and IV. As in earlier work with xanthonecarboxylic acids[12,13] and pyrido[2,1-*b*]-

(11) L. M. Jackman and R. H. Wiley, *Proc. Chem. Soc.*, 196 (1958); *J. Chem. Soc.*, 2886 (1960).
(12) J. R. Pfister, R. W. Ferraresi, I. T. Harrison, W. H. Rooks, A. P. Roszkowski, A. Van Horn, and J. H. Fried, *J. Med. Chem.*, 15, 1032 (1972).

quinazolinecarboxylic acids,[2,3] high activity was found for derivatives substituted with alkoxy, alkylthio, and alkyl substituents. The 6-substituted compounds were most extensively examined because of experience in the pyrido[2,1-b]quinazoline series. The most potent analogues in Table III were the 6-isopropoxy, 6-methylthio, 6-isopropyl, and the 6,8-diisopropyl compounds. Methyl esters **4d** and **4h** were less active than the corresponding acids. The sulfoxide **18** and sulfone **19** were somewhat less potent than the corresponding methylthio compound (**5i**). Compounds **5**, in which the propenoic acid side chain and the quinazoline can be coplanar, simulating the tricyclic pyrido[2,1-b]quinazolines (**1**), exhibited the highest activity. Methyl substitution at the 2-position in the quinazoline ring (**13**) or at the 3-position of the propenoic acid (**14**) would be expected to substantially destabilize the planar rotamer related to **1**, and both compounds were less active than the corresponding parent compounds **5l** and **5i**. An alternate explanation for the reduced activity of **14** is that the binding site cannot accomodate the additional methyl group. Unfortunately, the 9-methylpyrido[2,1-b]-quinazoline corresponding to **14** is not known. Molecular models of the *Z*-isomer **15** show the planar rotamers to be destabilized by steric interactions, and this compound was inactive. The propanoic acid analogue **16** with a conformationally flexible side chain was also inactive. The dihydroquinazoline **17** exhibited substantially reduced activity, perhaps due to loss of planarity of the ring system.

These structure–activity relationships parallel those found in a series of antiallergic 3-(4-oxo-4*H*-1-benzopyran-3-yl)acrylic acids (**20**),[14] where the *E* isomers were active but the *Z* isomers and the propanoic acids were inactive. This series (**20**) can be considered bicyclic analogues of the Syntex antiallergic xanthones (**21**).[12,13]



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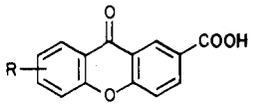

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Compounds **5i** and **5k** were orally active in a model in which anaphylactic bronchospasm was studied in passively sensitized rats[15] (ID_{50}'s of 0.02 and 0.05 mg/kg, respectively) and were potent inhibitors of antigen-induced histamine release from passively sensitized rat peritoneal cells in vitro[16] (IC_{50}'s of 0.25 and 0.19 μM, respectively). These and other pharmacological studies on (*E*)-3-[6-(methylthio)-4-oxo-4*H*-quinazolin-3-yl]-2-propenoic acid (**5i**) were reported elsewhere.[17]

In summary, the substituted (*E*)-3-(4-oxo-4*H*-quinazolin-3-yl)-2-propenoic acids exemplify a novel class of potent, orally active antiallergy agents.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Spectral data (IR, NMR, MS, and UV) were obtained for the new compounds and were in agreement with the assigned structures. Microanalytical data were determined on all new compounds and agree to within ±0.4% of the calculated values.

The required anthranilic acids were prepared as follows: 5-Methoxy-,[18] 5-(1-methylethoxy)-[18], 5-hydroxy-,[18] 5-(2-hydroxyethoxy)-,[18] 5-[2-(diethylamino)ethoxy]-,[18] 5-(1-methylethyl)-[19], 3,5-bis(1-methylethyl)-,[19] 3-methoxy-,[20] 3,5-dimethoxy-,[21] 4,5-dimethoxy-,[22] and 3,5-dimethylanthranilic acids[23] were prepared as described. 5-Chloroanthranilic acid was purchased from Aldrich Chemical Co. The 5-(methylthio)-, 5-[(1-methylethyl)thio]-, and the 5-cyclopropylanthranilic acids were prepared as described in this section.

2-Amino-5-(methylthio)benzoic Acid (8). Method A. A solution of 10.66 g (0.05 mol) 5-(methylthio)-2-nitrobenzoic acid[18] in 250 mL of EtOH and 0.5 g of 10% palladium on carbon was hydrogenated on a Parr shaker at an initial hydrogen pressure of 50 psi. After 3 h, uptake of hydrogen became very slow, and an additional 0.5 g of 10% Pd/C was added. The hydrogenation was continued for 16 h, at which time the reaction mixture was treated with 1 g of activated charcoal and stirred at room temperature for 45 min. After filtration through Celite, the filtrate was concentrated in vacuo, finally on the oil pump, to yield 8.77 g (96%), mp 150–154 °C (lit.[4] mp 145–150 °C), of tan solid **8** of sufficient purity for the next step.

Method B. To a suspension of 100.8 g (0.50 mol) of 5-chloro-2-nitrobenzoic acid in 1 L of H_2O was added 126 mL of 4.0 N NaOH. The solution (pH 7.5) was heated to 52 °C, and a suspension of 220 g (1.69 mol) of 60% Na_2S in 300 mL of H_2O was added in one portion. After the initial exotherm had subsided, the mixture was stirred at 52–55 °C for 2.5 h, at which time 100 mL of 20% NaOH was added. Dimethyl sulfate (95 mL, 1.0 mol) was then added dropwise over 10 min. The reaction mixture was stirred at reflux for 1 h and then cooled in an ice bath, and 60 mL of 12 N HCl was added dropwise. The solid was collected by filtration, washed with H_2O, and dried to give 80.4 g (88%) of **8**, mp 145–147.5 °C, of satisfactory purity for the next step. Recrystallization from ether gave material of mp 150–151 °C.

2-Amino-5-[(1-methylethyl)thio]benzoic acid. A mixture of 12.94 g (0.05 mol) of methyl 5-[(1-methylethyl)thio]-2-nitrobenzoate[18] and 12.9 g (0.23 g-atom) of iron powder in 100 mL of HOAc was stirred and heated on a steam bath for 3 h. The reaction mixture was cooled, diluted with 150 mL of toluene, and filtered. The filtrate was concentrated in vacuo to a dark oil, which was dissolved in 50 mL of MeOH and treated with 30 mL of 4.3 N HCl in MeOH. The solution was concentrated in vacuo, and the residue was crystallized from CH_2Cl_2–Et_2O to yield 10.70 g (81%), mp 128–129 °C, of methyl 2-amino-5-[(1-methylethyl)-thio]benzoate hydrochloride. Anal. ($C_{11}H_{15}NO_2S$·HCl) C, H, N; S: calcd, 12.25; found, 11.71. Cl^-: calcd, 13.54; found, 13.90. Hydrolysis with excess 1 N NaOH at room temperature for 19 h gave 2-amino-5-[(1-methylethyl)thio]benzoic acid, mp 123–124 °C, in 93% yield. Anal. ($C_{10}H_{13}NO_2S$) C, H, N, S.

***N*-(2-Bromo-4-cyclopropylphenyl)acetamide.** To 15.20 g (0.087 mol) of *N*-(4-cyclopropylphenyl)acetamide[24] and 10.45 g (0.177 mol) of acetamide dissolved in 1 L of $CHCl_3$ cooled and stirred at −25 °C was added dropwise a solution of 13.8 g (0.086 mol) of bromine in 300 mL of $CHCl_3$ over 2 h. The reaction mixture was stirred at −25 °C for 70 h and then allowed to warm to 5 °C. After filtration to remove the precipitate, the filtrate was concentrated in vacuo. The residue was chromatographed on 1.2 kg of silica gel. Elution with 40% ethyl acetate–toluene gave 11.22 g (51%), mp 108.5–110 °C, of *N*-(2-bromo-4-cyclo-

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propylphenyl)acetamide. In the NMR spectrum ($CDCl_3$), the cyclopropyl protons appeared at δ 0.65 (m, 2), 0.92 (m, 2), 1.82 (m, 1). Anal. ($C_{11}H_{12}NOBr$) H, N, Br; C: calcd, 51.99; found, 51.06.

***N*-(2-Cyano-4-cyclopropylphenyl)acetamide.** A solution of 11.22 g (0.044 mol) of *N*-(2-bromo-4-cyclopropylphenyl)acetamide and 8.96 g (0.1 mol) of cuprous cyanide in 500 mL of anhydrous DMF was stirred at reflux for 3 h. The DMF was removed in vacuo, and the residue was stirred with 15 mL of ethylene diamine in 500 mL of water for 30 min and then extracted with EtOAc. The dried ($MgSO_4$) extract was concentrated in vacuo to a solid, which was recrystallized from ethyl acetate–hexane to give 6.45 g (72%), mp 140–141 °C, of *N*-(2-cyano-4-cyclopropylphenyl)acetamide. In the NMR spectrum ($CDCl_3$), the cyclopropyl protons appeared at δ 0.68 (m, 2), 1.02 (m, 2), 1.87 (m, 1). Anal. ($C_{12}H_{12}N_2O$) C, H, N.

2-Amino-5-cyclopropylbenzoic Acid and 6-Cyclopropyl-2-methylquinazolin-4(3*H*)-one. To a solution of 6.30 g (0.03 mol) of *N*-(2-cyano-4-cyclopropylphenyl)acetamide in 120 mL of ethylene glycol–water (1:1) was added 8.86 g (0.16 mol) of KOH, and the reaction mixture was stirred at reflux for 19 h. The reaction mixture was cooled, 1 L of water was added, and the precipitate was filtered and recrystallized from ethyl acetate–hexane to give 1.20 g (20%), mp 236–237 °C, of 6-cyclopropyl-2-methylquinazolin-4(3*H*)-one. Anal. ($C_{12}H_{12}N_2O$) C, H, N.

The above aqueous solution was extracted several times with EtOAc, and the basic aqueous layer was acidified with HOAc and extracted with EtOAc. The dried (Na_2SO_4) extract was concentrated in vacuo to a solid, which was recrystallized from ether–hexane to yield 2.31 g (43%), mp 157.5–158.5 °C, of 2-amino-5-cyclopropylbenzoic acid. Anal. ($C_{10}H_{11}NO_2$) C, H, N.

6-(Methylthio)quinazolin-4(3*H*)-one (3i). A mixture of 55.0 g (0.30 mol) of 2-amino-5-(methylthio)benzoic acid and 48 mL (1.2 mol) of formamide was stirred mechanically under a take-off head and heated at 140–145 °C under an argon atmosphere. The mixture soon became a solid mass that was difficult to stir. After heating for 4 h, the reaction mixture was cooled, and 1 L of water was added. The solid was removed by filtration and recrystallized from MeOH to give 53.2 g (92%), mp 202–203 °C, of **3i**.

Methyl (*E*)-[6-(Methylthio)-4-oxo-4*H*-quinazolin-3-yl]-2-propenoate (4h). Sodium Hydride Procedure. Sodium hydride (0.205 g, 4.9 mmol, 57% oil dispersion) was stripped of oil with hexane and suspended in 15 mL of anhydrous DMF. A solution of 0.720 g (3.7 mmol) of **3i** in 10 mL of anhydrous DMF was added dropwise over 10 min to the sodium hydride with stirring under argon at room temperature. The reaction mixture was stirred and heated at 50 °C for 30 min and then cooled to room temperature. A solution of 0.497 g (4.1 mmol) of **12**[5] in 5 mL of anhydrous DMF was added dropwise over 10 min with stirring. The reaction mixture was then heated at 50 °C for 1 h. The solvent was removed in vacuo on the oil pump, and water was added to the residue. Filtration of the resultant solid and recrystallization from CH_2Cl_2–MeOH yielded 0.700 g (68%), mp 169–170 °C, of **4h**. Anal. ($C_{13}H_{12}N_2O_3S$) C, H, N; S: calcd, 11.61; found, 12.27.

Potassium Carbonate Procedure. A mixture of 48.1 g (0.25 mol) of **3i**, 33.1 g (0.275 mol) of **11**[5] and 51.8 g (0.375 mol) of anhydrous K_2CO_3 in 1.3 L of anhydrous acetone and 125 mL of anhydrous DMF was stirred mechanically at reflux for 18 h. The reaction mixture was concentrated in vacuo, finally on the oil pump, to remove most of the solvent, and water (2 L) was added to the residue. Filtration of the resultant solid and recrystallization from CH_2Cl_2–MeOH gave 58.2 g, mp 169–170 °C, of **4h**. A second crop of 4.2 g, mp 165–168 °C, was obtained from the filtrate, making the combined yield 90%.

(*E*)-3-[6-(Methylthio)-4-oxo-4*H*-quinazolin-3-yl]-2-propenoic Acid (5i). A suspension of 5.00 g (0.018 mol) of **4h** in 50 mL of 6 N HCl and 0.5 mL of 1-octanol was stirred vigorously and heated rapidly to reflux in a preheated oil bath. Reflux temperature was reached in 4 min and was maintained for 26 min. After the suspension was cooled, 200 mL of ice–water was added. The suspension was cooled for an additional 1 h, and the solid was filtered to give 4.06 g. This was stirred in 75 mL of water, and 2.0 mL of concentrated NH_4OH was added. The residual ester was removed by extraction with CH_2Cl_2. Acidification of the aqueous layer with concentrated HCl to pH 2.3 with stirring and filtration of the resultant solid gave 3.83 g (81%), mp 272–274 °C, of **5i**. In the NMR spectrum, the olefinic protons appeared as doublets (J = 15 Hz) at δ 6.68 and 8.17.

(*E*)-3-(6-Hydroxy-4-oxo-4*H*-quinazolin-3-yl)-2-propenoic Acid (5e). To 2.73 g (0.017 mol) of **3e** in 110 mL of anhydrous DMF stirred at room temperature was added 2.6 mL (0.019 mol) of triethylamine, followed by 2.6 mL (0.020 mol) of chlorotrimethylsilane, added dropwise over 10 min. The mixture was stirred for 2 h, and the triethylamine hydrochloride was removed by filtration. The filtrate was added in one portion to 1.06 g (0.025 mol) of a 57% oil dispersion of NaH which had previously been freed of oil by washing with pentane. The reaction mixture was stirred and heated under an argon atmosphere at 50 °C for 90 min. The mixture was cooled to 25 °C, and 2.02 g (0.017 mol) of **12** in 10 mL of anhydrous DMF was added dropwise over 15 min with stirring. The reaction mixture was stirred and heated at 50 °C for 2 h, and the DMF was then removed in vacuo. Water was added to give a solid, which was filtered and recrystallized from EtOAc–MeOH to yield 2.73 g (67%) of **4e**.

A mixture of 8.35 g (0.034 mol) of the above methyl ester and 500 mL of 6 N HCl was stirred at reflux for 15 min. After the mixture was cooled, the resultant solid was filtered to yield 6.33 g (81%), mp 294–296 °C, of **5e**.

(*E*)-3-[6-(2-Hydroxyethoxy)-4-oxo-4*H*-quinazolin-3-yl]-2-propenoic Acid (5f). To 2.048 g (0.01 mol) of **3f** in 60 mL of anhydrous DMF stirred at room temperature was added 1.52 mL (0.011 mol) of triethylamine, followed by 1.40 mL (0.011 mol) of chlorotrimethylsilane added dropwise over 5 min. The reaction mixture was stirred at room temperature for 90 min, and the triethylamine hydrochloride was removed by filtration. The filtrate was added to 0.643 g (0.015 mol) of 57% NaH which had previously been washed with hexane to remove the oil. The reaction mixture was stirred and heated under an argon atmosphere at 50 °C for 45 min. After cooling to 25 °C, 1.365 g (0.011 mol) of **12** in 2 mL of DMF was added dropwise over 10 min. The reaction mixture was stirred and heated at 50 °C for 75 min, and the DMF was then removed in vacuo. Hydrochloric acid (50 mL, 6 N) was added, and the mixture was stirred at reflux for 15 min. The mixture was cooled, and the resultant solid was filtered, washed well with water, and dried to yield 0.961 g (35%), mp 247–248 °C, of **5f**.

(*E*)-(6-Cyclopropyl-2-methyl-4-oxo-4*H*-quinazolin-3-yl)-2-propenoic Acid (13). A solution of 2.00 g (0.01 mol) of 6-cyclopropyl-2-methylquinazolin-4(3*H*)-one in 15 mL of anhydrous DMF was added dropwise over 15 min to a suspension of 84 mg (0.0105 mol) of lithium hydride in 15 mL of anhydrous DMF at 25 °C. The reaction mixture was stirred at room temperature for 30 min, then heated at 50 °C for 30 min, and then cooled to 25 °C. A solution of 1.33 g (0.011 mol) of **12** in 5 mL of anhydrous DMF was added dropwise over 10 min, and the mixture was then heated at 50 °C for 3 h. The reaction mixture was concentrated on the oil pump to remove the DMF. Water was added to the residue, and the resultant solid was filtered and recrystallized from CH_2Cl_2–MeOH to give 2.11 g (74%), mp 127.5–128 °C, of methyl (*E*)-(6-cyclopropyl-2-methyl-4-oxo-4*H*-quinazolin-3-yl)-2-propenoate. Anal. ($C_{16}H_{16}N_2O_3$) C, H, N.

A suspension of 0.28 g of the above methyl ester in 10 mL of 6 N HCl was stirred and heated at reflux for 10 min. Water (100 mL) was added, the mixture was cooled, and the solid was filtered and recrystallized from ethyl acetate–hexane to give 0.10 g (37%), mp 213.5–214 °C, of **13**. Anal. ($C_{15}H_{14}N_2O_3$) C, H, N.

(*E*)-3-[6-(Methylthio)-4-oxo-4*H*-quinazolin-3-yl]-3-methyl-2-propenoic Acid (14). A mixture of 4.81 g (0.025 mol) of **3i**, 5.57 g (0.0375 mol) of ethyl (*E*)-3-chloro-2-butenoate[25] (containing about 25% of the *Z* isomer), and 5.18 g (0.0375 mol) of anhydrous K_2CO_3 in 125 mL of anhydrous acetone and 12 mL of anhydrous DMF was stirred at reflux for 16 h. The reaction mixture was concentrated in vacuo, and 200 mL of water was added to the residue. Filtration of the resultant solid and recrystallization from CH_2Cl_2–MeOH gave 3.17 g (41%), mp 149–150 °C, of ethyl (*E*)-3-[6-(methylthio)-4-oxo-4*H*-quinazolin-3-yl]-3-methyl-2-propenoate. Anal. ($C_{15}H_{16}N_2O_3S$) C, H, N, S.

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A suspension of 3.04 g (0.01 mol) of the above ethyl ester in 85 mL of 6 N HCl was stirred at reflux for 30 min. Water (500 mL) was added, and, after cooling, the solid was filtered and washed with water to yield 2.28 g (83%), mp 216.5–218 °C, of **14**. Anal. ($C_{13}H_{12}N_2O_3S$) C, H, N, S. In the NMR spectrum, the vinylic methyl appeared as a doublet ($J \approx 1$ Hz) at δ 2.46, and the vinyl proton appeared as a multiplet at δ 6.13.

Photoisomerization of 14. A solution of 41.4 mg of **14** in 0.5 mL of Me_2SO-d_6 in an NMR tube was irradiated with a fluorescent desk lamp for 64 h. In the NMR spectrum, the vinylic methyl of the major isomer appeared as a doublet ($J \approx 1$ Hz) at δ 2.25, and the vinyl proton appeared as a multiplet at δ 6.26. The ratio of isomers based on the NMR spectrum was 2:1 (*Z*/*E*).

(*Z*)-3-[6-(Methylthio)-4-oxo-4*H*-quinazolin-3-yl]-2-propenoic Acid (15). A solution of 2.00 g of **5i** in 200 mL of DMF in a pyrex glass tube was irradiated with four fluorescent bulbs contained in two desk lamps for 40 h. HPLC analysis indicated the following ratio of *Z*/*E* isomers: 73:27 (18 h), 77:23 (22 h), 81:19 (40 h). The solution was concentrated in the dark in vacuo, and H_2O was added to the residue. Filtration gave 1.88 g of light tan solid. A portion (1.4 g) of this was dissolved in aqueous ammonium hydroxide and purified by HPLC on a Waters C-18 reverse-phase Prep column with 25% MeOH in 0.1 M NH_4OAc. Two center fractions (98% *Z* isomer) were combined and concentrated in vacuo to dryness. Water was added to the residue, followed by 1 N HCl to pH 3, and the precipitate was filtered. Recrystallization from pyridine gave 0.22 g of **15**, mp 233–234 °C. Anal. ($C_{12}H_{10}N_2O_3S$) C, H, N, S. The olefinic protons appeared as doublets (J = 9 Hz) at δ 6.12 and 7.30.

(*E*)-3-[1,4-Dihydro-6-(methylthio)-4-oxo-3(2*H*)-quinazolinyl]-2-propenoic Acid (17). To a stirred suspension of 0.525 g (0.002 mol) of **5i** in 20 mL of anhydrous THF cooled at −20 °C was added 2.0 mL (0.002 mol) of 1 M diborane in THF dropwise over 10 min. The suspension was stirred at −15 °C for 1 h and then allowed to warm to 25 °C over an additional 1 h. The solution was concentrated in vacuo to dryness, and the residue was treated with water (20 mL), followed by 15 mL of 6 N HCl. The orange solid was filtered to give 0.50 g, which was recrystallized from pyridine and then from methanol to yield 0.178 g (34%), mp 235–236 °C, of **17**. Anal. ($C_{12}H_{12}N_2O_3S$) C, H, N, S. The NMR spectrum (Me_2SO) exhibited a two-portion singlet at δ 4.90 for the ring methylene with a broad absorption beneath it for the ring NH and two doublets (J = 12 Hz) at δ 5.51 and 8.25 for the propenoic side chain.

6-(Methylthio)-4-oxo-4*H*-quinazoline-3-propanoic Acid (16). A solution of 0.897 g (0.0034 mol) of **5i** in 30 mL of MeOH and 20 mL of H_2O containing 2.0 mL of concentrated NH_4OH and 1.0 g of 10% palladium on carbon was shaken at 50 psi in a Parr hydrogenation apparatus for 17 h. An additional 1.0 g of catalyst was added, and the hydrogenation was continued for 23 h. The catalyst was removed by filtration through Celite, and the filtrate was concentrated to dryness in vacuo. The residue was dissolved in 30 mL of H_2O, and the solution was acidified with HOAc. The resultant precipitate was filtered and recrystallized from MeOH to yield 0.381 g (42%), mp 190–191 °C, of **16**. Anal. ($C_{12}H_{12}N_2O_3S$) C, H, N, S. The NMR (Me_2SO-d_6) spectrum exhibited two proton triplets (J = 7 Hz) at δ 2.75 and at δ 4.17 for the propanoic acid side chain and a singlet at δ 8.32 for the quinazoline ring proton.

(*E*)-3-[6-(Methylsulfinyl)-4-oxo-4*H*-quinazolin-3-yl]-2-propenoic Acid (18). To a suspension of 5.20 g (0.02 mol) of **5i** in 250 mL of water was added 22 mL of 1 N NaOH (0.022 mol), followed by 5.10 g (0.024 mol) of sodium periodate. The reaction mixture was stirred at room temperature for 4.5 h, and the solution was acidified with 5 mL of HOAc. The product crystallized slowly on stirring and was filtered. Two recrystallizations from HOAc gave 2.94 g (53%), mp 281–283 °C, of **18**. Anal. ($C_{12}H_{10}N_2O_4S$) C, H, N, S.

(*E*)-3-[6-(Methylsulfonyl)-4-oxo-4*H*-quinazolin-3-yl]-2-propenoic Acid (19). A suspension of 2.00 g (7.6 mmol) of **5i** in 100 mL of HOAc and 1.72 mL (15.2 mmol) of 30% H_2O_2 was stirred and heated in an oil bath at 105 °C for 10 min. The bath temperature was lowered to 55 °C, and heating was continued for 6 h. After the solution was cooled to 25 °C the solid that had precipitated was filtered and recrystallized from HOAc to yield 1.54 g (69%), mp 288–294 °C, of **19**. Anal. ($C_{12}H_{10}N_2O_5S$) C, H, N, S.

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Registry No. **2** (R = H), 118-92-3; **2** (R = 5-OCH_3), 6705-03-9; **2** (R = 3-OCH_3), 3177-80-8; **2** [R = 5-$OCH(CH_3)_2$], 68701-42-8; **2** (R = 5-OH), 394-31-0; **2** [R = 5-$O(CH_2)_2OH$], 78299-60-2; **2**·HCl [R = 5-$O(CH_2)_2N(C_2H_5)_2$], 84117-88-4; **2** (R = 5-Cl), 635-21-2; **2** [R = 5-$SCH(CH_3)_2$], 84117-89-5; **2** [R = 5-$CH(CH_3)_2$], 68701-22-4; **2** (R = 5-cyclopropyl), 68701-47-3; **2** [R = 4,5-$(OCH_3)_2$], 5653-40-7; **2** [R = 3,5-$(OCH_3)_2$], 79263-00-6; **2** [R = 3,5-$(CH_3)_2$], 14438-32-5; **2** [R = 3,5-$[CH(CH_3)_2]_2$], 79069-40-2; **3a**, 491-36-1; **3b**, 19181-64-7; **3c**, 16064-27-0; **3d**, 78299-54-4; **3e**, 16064-10-1; **3f**, 78299-61-3; **3g**, 84117-90-8; **3h**, 16064-14-5; **3i**, 78299-51-1; **3j**, 84117-91-9; **3k**, 78299-42-0; **3l**, 78299-45-3; **3m**, 13794-72-4; **3n**, 79263-01-7; **3o**, 79263-04-0; **3p**, 79262-95-6; **4a**, 79263-07-3; **4b**, 78299-11-3; **4c**, 79262-98-9; **4d**, 78299-55-5; **4e**, 78299-66-8; **4f**, 78312-83-1; **4g**, 78299-48-6; **4h**, 78299-52-2; **4i**, 84117-92-0; **4j**, 78312-82-0; **4k**, 78299-46-4; **4l**, 84117-93-1; **4m**, 79263-02-8; **4n**, 79263-05-1; **4o**, 79262-96-7; **5a**, 79263-08-4; **5b**, 78299-12-4; **5c**, 79262-99-0; **5d**, 78299-56-6; **5e**, 78299-67-9; **5f**, 78299-62-4; **5g**, 84117-94-2; **5h**, 78299-49-7; **5i**, 78299-53-3; **5j**, 84117-95-3; **5k**, 78299-43-1; **5l**, 78299-47-5; **5m**, 84117-97-5; **5n**, 79263-03-9; **5o**, 79263-06-2; **5p**, 79262-97-8; **6**, 2516-95-2; **7**, 68701-32-6; **8**, 76745-74-9; **11**, 3510-44-9; **12**, 5135-18-2; **13**, 84117-98-6; (*E*)-**14**, 84117-99-7; (*Z*)-**14**, 84118-00-3; **15**, 84118-01-4; **16**, 84118-02-5; **17**, 84118-03-6; **18**, 78299-68-0; **19**, 78312-84-2; methyl 5-[(1-methylethyl)thio]benzoate, 84118-04-7; *N*-(2-bromo-4-cyclopropylphenyl)acetamide, 68701-45-1; *N*-(4-cyclopropylphenyl)acetamide, 19936-11-9; *N*-(2-cyano-4-cyclopropylphenyl)acetamide, 68701-46-2; 6-cyclopropyl-2-methylquinazolin-4(3*H*)-one, 84118-05-8; formamide, 75-12-7; methyl (*E*)-(6-cyclopropyl-2-methyl-4-oxo-4*H*-quinazolin-3-yl)-2-propenoate, 84118-06-9; ethyl (*E*)-3-chloro-2-butenoate, 6127-92-0; ethyl (*Z*)-3-chloro-2-butenoate, 6127-93-1; ethyl (*E*)-3-[6-(methythio)-4-oxo-4*H*-quinazolin-3-yl]-3-methyl-2-propenoate, 84118-07-0.