stirring to a solution of the bisketimine **27** (0.38 g, 1 mmol) in dry THF (10 mL) at -78 °C under nitrogen. Diethyl oxalate (0.15 mL, 1.1 mmol) was added and the mixture allowed to warm to room temperature. The reaction mixture was added to ethanol (50 mL) and concentrated HCl (5 mL), the mixture was stirred for a further 4 h, and volatiles were removed in vacuo. The product was extracted into $CHCl_3$, washed with water, dried, and evaporated. The residue was chromatographed on silica gel, eluting with petrol/EtOAc (1:1) and recrystallized to give **28**: 0.3 g (78%); mp 159–163 °C; NMR ($CDCl_3$) δ 0.97 (6 H, 2 t), 1.44 (3 H, t), 1.73 (8 H, m), 2.74 (3 H, s), 3.33 (4 H, m), 4.47 (2 H, q), 5.35 (1 H, br s), 7.03 (1 H, s), 8.17 (1 H, s).

Diethyl 4-Oxo-6-(pentylamino)-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (29). A solution of sodium ethoxide, from sodium (0.1 g, 4.3 mmol) in ethanol (10 mL), was added to a mixture of ester **28** (0.95 g, 2.46 mmol) and diethyl oxalate (0.6 mL, 4.4 mmol) in dry ethanol (10 mL). The reaction mixture was heated under reflux for 10 min, cooled, and acidified with ethanolic HCl. After further heating for 2 h and evaporation of volatiles, the product was taken into CH_2Cl_2, washed with dilute aqueous ammonia, dried, and evaporated. Recrystallization from ethanol gave **29**: 0.67 g (58%); NMR ($CDCl_3$) δ 1.03 (6 H, 2 t), 1.50 (6 H, 2 t), 1.75 (8 H, m), 3.50 (4 H, m), 4.47 (4 H, 2 q), 7.03 (1 H, s), 7.13 (1 H, s), 8.68 (1 H, s).

Disodium 4-Oxo-6-(pentylamino)-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (34). Diester **29** was hydrolyzed in the standard manner to give **34**: NMR (DMSO-d_6) δ 0.89 (6 H, t), 1.40 (4 H, m), 1.75 (4 H, m), 3.45 (4 H, m), 6.60 (1 H, s), 6.86 (1 H, s), 8.85 (1 H, s). Anal. ($C_{22}H_{22}N_2Na_2O_6 \cdot 13\%$ H_2O) C, H, N.

Acknowledgment. We thank P. A. Cage, D. Cox, I. D. Dicker, H. A. Dowlatshahi, S. King, I. Sharma, J. Shipman, and R. G. McR Wright for assistance with chemical synthesis and S. T. Harper for biochemical support.

Registry No. **2**, 69049-59-8; **3**, 99370-25-9; **4**, 99370-26-0; **5**, 114184-12-2; **6**, 99370-27-1; **7**, 75453-75-7; **8**, 114184-13-3; **9**, 114184-14-4; **10**, 75452-74-3; **11**, 114184-15-5; **12**, 99370-84-0; **13**, 114184-16-6; **14**, 114184-17-7; **15**, 99370-45-3; **16**, 114184-18-8; **17**, 114184-19-9; **18**, 114184-20-2; **19**, 86694-89-5; **20**, 114184-21-3; **21**, 114184-22-4; **22**, 75452-57-2; **23**, 114184-23-5; **24**, 75453-51-9; **25**, 75453-52-0; **26**, 79324-47-3; **27**, 114184-24-6; **28**, 114184-25-7; **29**, 114184-26-8; **30**, 75453-49-5; **31**, 98331-60-3; **32**, 75452-62-9; **33**, 75453-37-1; **34**, 114184-27-9; **35**, 114184-28-0; **36**, 98331-59-0; **37**, 75453-53-1; **38**, 114184-29-1; **39**, 75453-25-7; **40**, 114184-30-4; **41**, 114184-31-5; **42**, 75452-76-5; **43**, 75453-70-2; **44**, 98331-58-9; **45**, 99369-73-0; **46**, 75453-59-7; **47**, 114184-32-6; **48**, 114184-33-7; **49**, 75452-70-9; **50**, 75452-50-5; **51**, 99369-81-0; **52**, 75452-65-2; **53**, 114184-34-8; **54**, 114184-35-9; **55**, 114184-36-0; **56**, 99369-72-9; **57**, 75453-28-0; **58**, 99369-71-8; **59**, 114184-37-1; **60**, 75453-62-2; 2,5-dimethoxytetrahydrofuran, 696-59-3.

4-Hydroxy-3-quinolinecarboxamides with Antiarthritic and Analgesic Activities

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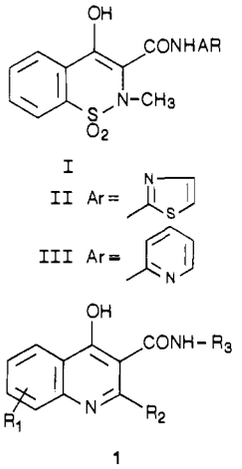
A series of 4-hydroxy-3-quinolinecarboxamides has been synthesized and evaluated by the oral route as antiinflammatory agents in carrageenin-induced foot edema and adjuvant-induced arthritis and as analgesic agents in the acetic acid induced writhing test. Among the most active molecules, some have shown both analgesic and acute antiinflammatory activities. Others, such as compounds **24**, **37**, and **52**, were only powerful peripherally acting analgesics. Compound **52**, being active at 1 mg/kg (ED_{50}), is the most potent compound in the series. Some analogues, substituted in the 2-position by an alcohol, ester, or amine function, displayed potent antiarthritic activity in the same range as that of piroxicam and were also active in acute tests of inflammation and nociception. They inhibited the activity of both cyclooxygenase and 5-lipoxygenase at micromolar concentrations. Compound **102** (RU 43526) showed potent antiarthritic activity (adjuvant-induced arthritis, ED_{50} = 0.7 mg/kg, po) and gastrointestinal tolerance (ED_{100} > 250 mg/kg, po) and thus it is presently undergoing an extensive pharmacological evaluation.

Since the discovery of indomethacin and ibuprofen in the 1960s, extensive research has been undertaken in many laboratories in order to find new highly potent nonsteroidal antiinflammatory agents with weak side effects. Although most of these compounds give only palliative treatment of arthritis, numerous papers still deal with the synthesis and evaluation of the antiinflammatory and analgesic activities of new leads (for reviews, see ref 1–3). At the beginning of the last decade a wide-ranging program was initiated in our company, the objective of which was to develop new nonsteroidal antiinflammatory compounds that are well tolerated at the gastrointestinal level. First of all, we carried out work in the field of arylacetic acids[4] but soon turned our attention to the work of Lombardino et al.,[5] which led to the discovery of the new class of oxicams (I) of which sudoxicam (II) and piroxicam (III) are the prototypes.[6]

For a long time our research group had been interested in quinoline chemistry[7] and this situation prompted us to study 4-hydroxy-3-quinolinecarboxamides **1**, which could



1

actually be regarded as possible bioisosteres of oxicams I. Furthermore, the antiarthritic potency of the antimalarial

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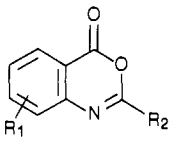
‡ Department of Biology.

(1) For a review and references, see: Lombardino, J. G. *Annual Reports in Medicinal Chemistry*; Hess, H. J., Ed.; Academic: New York, 1981; p 189.

0022-2623/88/1831-1453$01.50/0

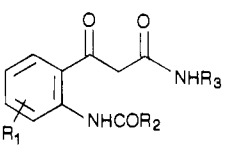
Table I



compd	C[a]	R_1	R_2	yield, %	mp, °C	cryst[b] solv	anal.
4a		H	$CHClCH_3$	92	90–92	EP	C,H,N,Cl
4b		6-CF_3	CF_3	90	104–105	EP	C,H,N,F
4c		8-SCF_3	CF_3	100	45–47	*c*	C,H,N,F,S
4d		7-Cl	$CHCl_2$	83	119–120	EE	C,H,N,Cl
4e		8-CF_3	$CHClC_2H_5$	97	71–72	EP	*d*
4f		8-CF_3	$CHCl(CH_2)_2CH_3$	78	75–77	EP	C,H,N,Cl,F
4g		8-CF_3	$CHClCH(CH_3)_2$	78	79–80	EP	C,H,N,Cl,F
4h		8-CF_3	$CHCl(CH_2)_3CH_3$	53	oil	*e*	*d*
4i		8-CF_3	$CHClC(CH_3)_3$	69	103–104	*f*	C,H,N,Cl,F
4j		8-CF_3	CHCl-c-C_6H_{11}	77	84–86	EP	C,H,N,Cl,F
4k		8-CF_3	$CHCl-C_6H_5$	75	88–90	EP	C,H,N,Cl,F
4l	*S*	8-CF_3	$CH(NH\text{-}Boc)CH_3$	57	172–174	M	C,H,N,F
4m	*R*	8-CF_3	$CH(NH\text{-}Boc)CH_3$	49	174–176	*f*	*d*
4n	*S*	8-CF_3	$CH(NH\text{-}Boc)C_2H_5$	53	135–138	*f*	C,H,N,F
4o	*S*	8-CF_3	$CH(NH\text{-}Boc)CH(CH_3)_2$	39	164–165	*f*	*d*

[a] Absolute configuration. [b] Key: EE, ethyl ether; EP, petroleum ether; M, methyl alcohol. [c] Sublimated. [d] No analysis. [e] Purified by column chromatography on silica gel: ethyl acetate–petroleum ether. [f] Crude product.

Table II



compd	C[a]	R_1	R_2	R_3	yield, %	mp, °C	cryst[b] solv	anal.
6a		H	$CHClCH_3$	2-thiazolyl	74	204–206	A	C,H,N,Cl,S
6b		4-Cl	$CHCl_2$	2-thiazolyl	56	180–182	*c*	*d*
6c		3-CF_3	$CHClC_2H_5$	2-thiazolyl	79	190–191	*c*	*d*
6d		3-CF_3	$CHCl(CH_2)_2CH_3$	2-thiazolyl	81	193–195	A	C,H,N,Cl,F,S
6e		3-CF_3	$CHClCH(CH_3)_2$	2-thiazolyl	82	188–189	A	C,H,N,Cl,F,S
6f		3-CF_3	$CHCl(CH_2)_3CH_3$	2-thiazolyl	73	188–190	A	C,H,N,Cl,F,S
6g		3-CF_3	$CHClC(CH_3)_3$	2-thiazolyl	82	206–207	A	C,H,N,Cl,F,S
6h		3-CF_3	CHCl-c-C_6H_{11}	2-thiazolyl	79	228–229	*c*	*d*
6i		3-CF_3	$CHClC_6H_5$	2-thiazolyl	66	183–185	EE	C,H,N,Cl,F,S
6j	*S*	6-CF_3	$CH(NH\text{-}Boc)CH_3$	2-thiazolyl	94		*c*	*d*
6k	*R*	6-CF_3	$CH(NH\text{-}Boc)CH_3$	2-thiazolyl	93		*c*	*d*
6l	*S*	6-CF_3	$CH(NH\text{-}Boc)C_2H_5$	2-thiazolyl	59	189–191	MC	*d*
6m	*S*	6-CF_3	$CH(NH\text{-}Boc)CH(CH_3)_2$	2-thiazolyl	93	119–121	*c*	*d*
6n		3-CF_3	$CHClCH_3$	2-pyridyl	58	150–151	*c*	*d*
6o		3-CF_3	$CHClC_2H_5$	2-pyridyl	63	137	*c*	*d*
6p		3-CF_3	$CHClCH(CH_3)_2$	2-pyridyl	72	135–138	EE	C,H,N,F,Cl

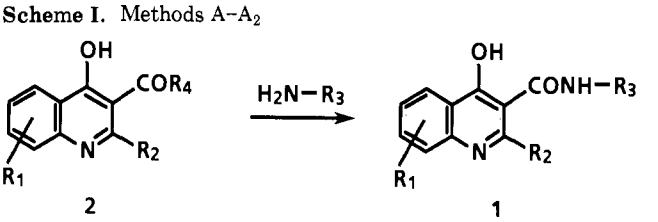
[a] Absolute configuration. [b] Key: A, acetonitrile; EE, ethyl ether; MC, methylene chloride. [c] Crude product. [d] No analysis.

chloroquine belonging to the quinoline series is well-known.[8] This paper describes the synthesis and pharmacological evaluation of various 4-hydroxy-3-quinolinecarboxamides.

Chemistry

4-Hydroxy-3-quinolinecarboxamides **1** were synthesized by the methods described earlier[9] and outlined in Schemes I and II (methods A and B). Depending on the nature of the substituents in position 2, amide formation was carried out with acids (method A), esters (method A1), or acid

Scheme I. Methods A–A_2



R_4 = OH (METHOD A)

R_4 = OC_2H_5 (METHOD A_1)

R_4 = Cl (METHOD A_2)

(2) Cullen, E. *J. Pharm. Sci.* **1984**, *73*, 579.
(3) Turner, R. A. *Drugs Today* **1984**, *20*, 639.
(4) Clemence, F.; Le Martret, O.; Fournex, R.; Plassard, G.; Dagnaux, M. *Eur. J. Med. Chem.-Chim. Ther.* **1974**, *9*, 390.
(5) Lombardino, J. G.; Wiseman, E. H.; Chiaini, J. *J. Med. Chem.* **1973**, *16*, 493.
(6) (a) Lombardino, J. G.; Wiseman, E. H. *Med. Res. Rev.* **1982**, *2*, 127. (b) See also: Zinnes, H.; Sircar, J. C.; Lindo, N.; Schwartz, M. L.; Fabian, A. C.; Shavel, J., Jr.; Kasulanis, C. F.; Genzer, J. D.; Lutomski, C.; Dipasquale, G. *J. Med. Chem.* **1982**, *25*, 12.
(7) Allais, A.; Rousseau, G.; Meier, J.; Nominé, G.; Peterfalvi, M.; Deraedt, R.; Chifflot, L.; Benzoni, J.; Fournex, R. *Eur. J. Med. Chem.-Chim. Ther.* **1973**, *8*, 154.
(8) MacKenzie, A. H. *Arthritis Rheum.* **1970**, *13*, 280.
(9) Clémence, F.; Le Martret, O.; Collard, J. *J. Heterocycl. Chem.* **1984**, *21*, 1345.

Scheme II. Method B

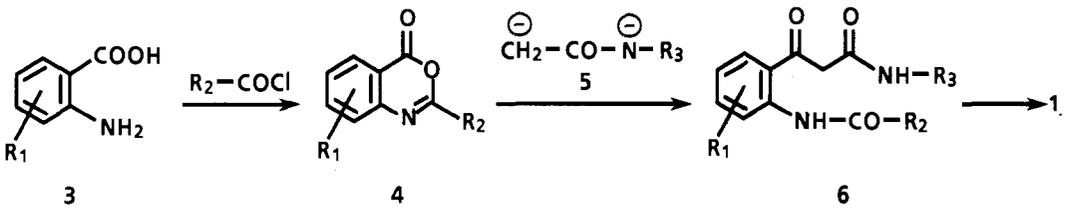
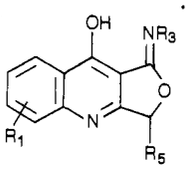


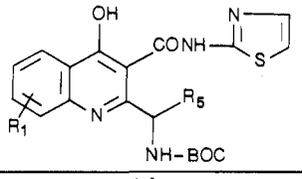
Table III



compd	R_1	R_5	R_3	yield, %	mp, °C	cryst[a] solv	anal.
8a	H	CH_3	2-thiazolyl	59	>270	*b*	*c*
8b	8-CF_3	C_2H_5	2-thiazolyl	71	250–251	D	C,H,N,F,S
8c	8-CF_3	$(CH_2)_2CH_3$	2-thiazolyl	100	238–240	*b*	*c*
8d	8-CF_3	$CH(CH_3)_2$	2-thiazolyl	100	248–249	*b*	*c*
8e	8-CF_3	$(CH_2)_3CH_3$	2-thiazolyl	100	228–229	*b*	*c*
8f	8-CF_3	$C(CH_3)_3$	2-thiazolyl	60	250–252	*b*	*c*
8g	8-CF_3	cyclohexyl	2-thiazolyl	100	275–276	*b*	*c*
8h	8-CF_3	phenyl	2-thiazolyl	100	270–271	*b*	*c*
8i	8-CF_3	CH_3	2-pyridyl	19	198–203	E	C,H,N,F
8j	8-CF_3	C_2H_5	2-pyridyl	73	172–173	*b*	*c*
8k	8-CF_3	$CH(CH_3)_2$	2-pyridyl	85	180–182	*b*	*c*

[a] Key: D, dioxane; E, ethyl alcohol. [b] Crude product. [c] No analysis.

Table IV



compd	C[a]	R_1	R_5	yield, %	mp, °C	cryst[b] solv	anal.
11a	*S*	CF_3	CH_3	50	267–268	M	C,H,N,F,S
11b	*R*	CF_3	CH_3	63	265–267	M	C,H,N,F,S
11c	*S*	CF_3	C_2H_5	88	259–262	EE	C,H,N,F,S
11d	*S*	CF_3	$CH(CH_3)_2$	73	222–223	EI	C,H,N,F,S

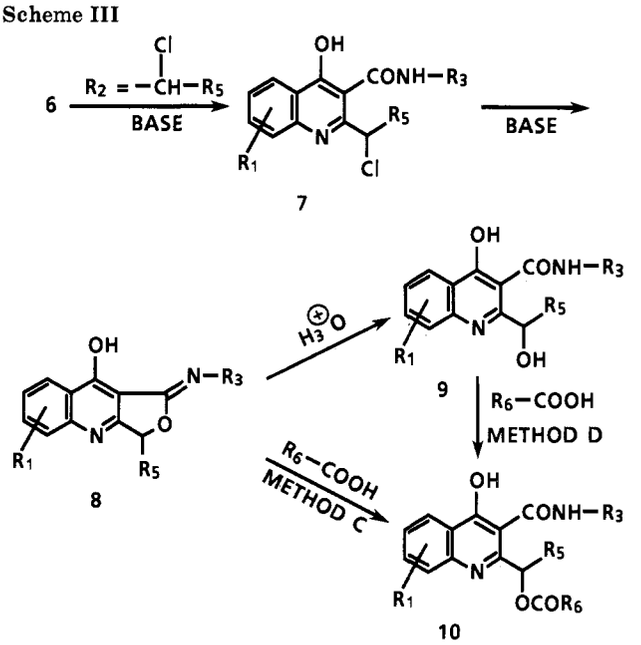
[a] Absolute configuration. [b] Key: EE, ethyl ether; EI, isopropyl ether; M, methyl alcohol.

chlorides (method A2). On the other hand, anthranilic acids **3** (Scheme II) led to 4*H*-3,1-benzoxazin-4-ones **4**. Reaction of these compounds with dianion **5** gave 2-(acylamino)-β-oxopropanamides **6**. Ring closure of **6** afforded the target compounds **1** (method B). Some new intermediates **4** and **6** not previously described[9] are listed in Tables I and II. Quinolinecarboxamides **9** bearing an alcohol function in position 2 (Table VI) were prepared by heating tricyclic products **8** (Table III) at reflux in aqueous hydrogen chloride (Scheme III). These latter compounds were obtained by cyclization of the 2-chloroalkyl derivatives **7**, which in turn were synthesized following method B. Usually, quinolinecarboxamides **7** were not isolated and were cyclized directly to **8**.[9]

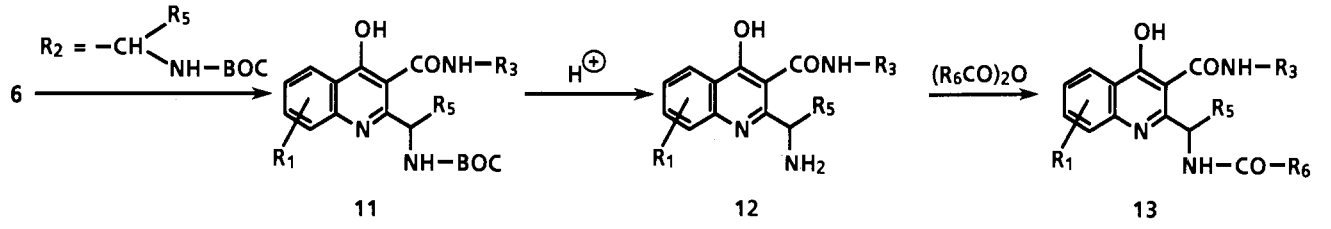
Heating **8** with carboxylic acids afforded esters **10** (Table VII) (method C). Moreover, **10** could be obtained by esterification of **9** (method D). Amino derivatives **11** (Table IV) were formed following method B from the corresponding Boc-amino acids (Scheme IV). Deprotection of **11** was accomplished by trifluoroacetic acid and amino quinolines **12** could be acylated if necessary (Table VIII).

Concerning the synthesis of amino derivatives **12**, it should be noted that the use of *S* or *R* Boc-amino acids

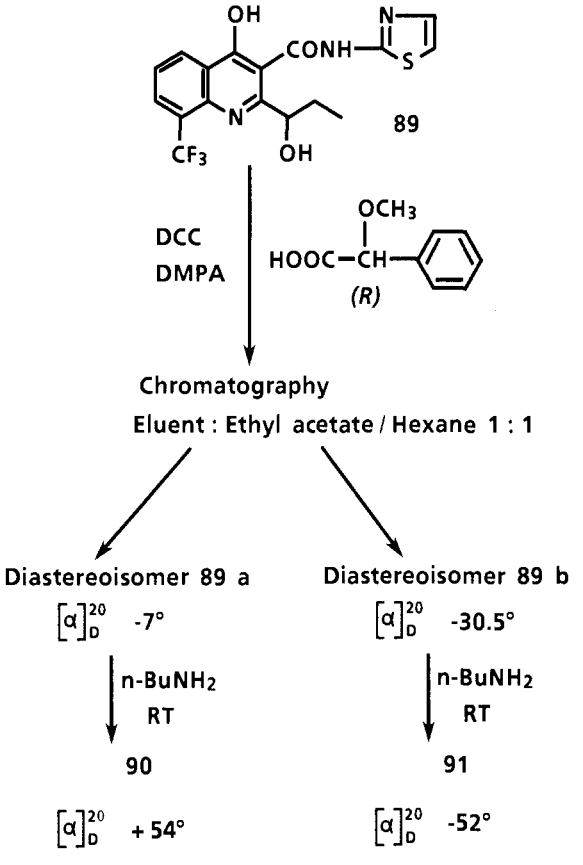
Scheme III



Scheme IV



Scheme V



enables *S* or *R* enantiomers of quinolinecarboxamides **12** to be easily prepared. On the other hand, the synthesis of 2-hydroxyalkyl-substituted quinolinecarboxamides **9** (Scheme III) leads to racemic derivatives. Thus compound **89**, one of the most active in this series, was resolved (Scheme V). Esterification of **89** with (*R*)-(−)-α-methoxyphenylacetic acid gave a mixture of diastereomeric esters (**89a** and **89b**), which were readily separable by column chromatography on silica gel. Aminolysis of these esters with *n*-butylamine led to the enantiomers (+)-**90** and (−)-**91**. Determination of the absolute configuration of these products by single-crystal X-ray analysis is under way.

Pharmacological Results and Discussion

The pharmacological activities of the compounds were determined by the oral route in the acetic acid induced writhing test in the mouse and in carrageenin-induced foot edema in the rat (Table V). Moreover, the activity of alcohols, esters, and amines in chronic inflammation (Tables VI–VIII) was evaluated by using the rat adjuvant-induced arthritis model (see the Experimental Section). The structure–activity relationships of these compounds may be discussed in three parts: (1) the aryl substituents, (2) the substituent on the amide nitrogen, and (3) the nature of the substituent in the 2-position of the quinoline.

Concerning the aryl substituents R_1 and from the viewpoint of analgesic activity, it soon became apparent that the trifluoromethyl group led to the most active compounds. Moreover, the 8-trifluoromethyl compound was more potent than the 6- or 7-trifluoromethyl isomers (compare **22**, **23**, and **24**). The nature of the heterocycle on the amide nitrogen had a pronounced effect on analgesic activity. In general, the most potent compounds contained a thiazole moiety (Table V). In a few cases, pyridine, oxazole, and imidazole moieties led to analogues with good activity (**47**, **49**, and **25**), but substitution of the amide function with other heterocycles produced less active or totally inactive compounds.

Nevertheless, the 4,5-dihydro-2-thiazolyl derivative **34** showed a fairly good analgesic activity and it is interesting to point out that derivatives of **34** have been studied in a different field following the discovery of their high affinity for the central benzodiazepine receptor.[10,11]

As we have seen above, thiazole is the most suitable aromatic ring, and with this heterocycle the best substituent R_1 on the benzene ring is CF_3 with the most favorable position being 8. As far as the nature of the substituent in the 2-position is concerned and when these functions (8-CF_3 and thiazole) are maintained, the following sequence can be established: methyl (**37**), ethyl (**38**), isopropyl (**41**), and hydrogen (**24**) gave about the same results, better than those of other alkyls and much better than those with phenyl (**46**) or benzyl (**45**) (Table V). On the other hand, we obtained a great improvement in activity with certain halogen radicals, such as dichloromethyl (**52**), difluoromethyl (**56**), or trifluoromethyl (**58**). However, apart from the influence of the substitution at the 2-position on the analgesic activity, another result worth noting is that these substitutions led either to products that are solely analgesic (hydrogen (**24**), alkyl groups (**37**, **38**), i.e., electron-donating groups) or mixed analgesic and antiinflammatory products (trifluoromethyl (**58**), difluoromethyl (**56**), pentafluoroethyl (**57**), i.e., electron-attracting groups).

With regard to the pharmacological activities of compounds substituted in the 2-position by an alcohol function (Table VI), the following can be stated. (1) The aliphatic alcohols were much more active than aryl- or cycloalkyl-substituted ones. In fact, **96** and **97** were inactive. In addition the primary alcohol (**87**) does not show any activity. (2) The secondary alcohols possess considerable activity in the adjuvant-induced arthritis test, which is more indicative of a chronic antiinflammatory activity (**88**, **89**, **93**, and **95**). These compounds were also very potent in inhibiting carrageenin paw edema. Moreover, compounds **88** and **89** displayed powerful peripheral analgesic activity. In addition, it could be noted that the antiar-

(10) Clémence, F.; Hunt, P.; Le Martret, O.; Humbert, D. Eur. Pat. Appl. EP 67,772, 1982; *Chem. Abstr.* **1983**, *98*, 179365*w*.

(11) Hunt, P.; Humbert, D.; Gasc, J. C.; Clémence, F.; Boaventura, A. M. *Proceedings of 8th International Symposium on Medicinal Chemistry; Uppsala, Sweden, August 27–31*; Swedish Pharmaceutical Press: Stockholm, 1984.

thritic and analgesic activity of racemate **89** is probably due to the (−) enantiomer, **91**. Taking into account the stereoselectivity of activity observed in bioisosteric aminoquinoline series (see below), we tentatively assign the *S* absolute configuration to compound **91**. (3) It is very interesting to note that esters of the most active alcohols were often very potent in the adjuvant arthritis test (Table VII: **102**, **104**, and **105**), whereas their potency in acute tests was rather low (see below) probably because of pharmacokinetics.

The isosteric replacement of oxygen by nitrogen in the most active alcohols led to a few amino quinolines with the same pharmacological profile (Table VIII). The most potent compounds belonged to the *S* series (compare **116** with **117**) and amide formation of **118** led to derivatives (**119**, **120**) with higher antiarthritic activities.

As shown in Table IX, this series of 4-hydroxy-3-quinolinecarboxamides exhibits a dual pharmacological potentiality after oral administration. Some compounds (**24** and **52**) are very potent peripherally acting analgesics; other (**58**, **89**, **102**, **118**, **120**) possess, in addition, high antiarthritic activities.

Peripherally Acting Analgesics: Compounds 24 and 52. Both compounds were effective in the acetic acid induced writhing test, their ED_{50}'s being 5 and 1.1 mg/kg, respectively. They were totally inactive at 100 mg/kg in the mouse hot-plate test (56 °C), which only detects central analgesics. Compound **24** displayed no antiinflammatory activity whereas compound **52** has an antiarthritic component (ED_{50} = 48 mg/kg). They were both very well tolerated by the gastrointestinal tract, especially **24**.

Antiinflammatory and Antiarthritic Compounds. Compounds **58**, **89**, **102**, **118**, and **120** showed potent activity in inhibiting the development of adjuvant-induced arthritis. The amino derivatives (**118** and **120**) were active at 3 mg/kg, the alcohol derivative (**89**) was twice as effective, and compound **102**, the propionate of **89**, displayed the highest activity with an ED_{50} of 0.7 mg/kg. It had the same potency as piroxicam. These molecules also exhibited acute antiinflammatory effects as shown by their activity in the carrageenin-induced edema model. They also had peripheral analgesic potential (it has been checked that they have no effect in the hot-plate test). Regarding compounds **102** and **120**, their analgesic activity depended on the time of administration before the chemical stimulus and greatly increased when the drug was given 6 h before the irritant instead of 30 min. The esterified derivatives were much better tolerated by the gastrointestinal tract than the alcohol or amino compounds. This was particularly obvious for compound **102**, which was at least 30 times better tolerated by the gastric and intestinal mucosa than compound **89**.

Action on Arachidonic Acid Metabolism. All compounds had potent inhibitory activities on cyclooxygenase, the enzyme that metabolizes arachidonic acid into endoperoxides and then into prostaglandins (PGs). Most of them are active in the micromolar range, with compounds **58**, **89**, and **120** being the most effective.

Unlike piroxicam, the antiinflammatory derivatives inhibited 5-lipoxygenase at micromolar concentrations (BW755c,[12] a compound that inhibits both cyclooxygenase and lipoxygenase, had an IC_{50} of 12 μM in this system).

In summary, a series of 4-hydroxy-3-quinolinecarboxamides has been synthesized, several members of which are inhibitors of arachidonic acid metabolism and active at low oral doses in models of chronic and acute inflammation. Two members of this series (**102** and **120**) have an excellent gastrointestinal tolerance that should give them a therapeutic index much higher than that of piroxicam. Moreover, compound **102** (RU 43526) is active in some models that are insensitive to selective inhibitors of cyclooxygenase (carrageenin, pleurisy; sheep red blood cell rosette formation). These compounds therefore may constitute attractive agents for the treatment of inflammatory diseases such as rheumatoid disorders.

Experimental Section

Chemistry. Melting points were determined on a Kofler or a Maquenne apparatus and are uncorrected. The structures of all compounds were confirmed by IR, UV, and ^1H NMR spectra. Spectral measurements were performed on the following instruments: IR on a Perkin-Elmer 580B, UV on a Cary 14 or 15, and NMR on a Varian T60, Brucker WP60, or WH90 spectrometer.

Method A. 4-Hydroxy-2-(1-methylethyl)-*N*-(2-thiazolyl)-8-(trifluoromethyl)-3-quinolinecarboxamide (41). A solution of 2-(1-methylethyl)-4-hydroxy-8-(trifluoromethyl)-3-quinolinecarboxylic acid[13] (6.3 g, 0.021 mol), 2-aminothiazole (2.1 g, 0.021 mol), and dicyclohexylcarbodiimide (4.74 g, 0.023 mol) in dimethylformamide (130 mL) was stirred at room temperature for 72 h. The mixture was filtered and evaporated in vacuo. The residue was triturated with a 5% sodium hydrogen carbonate solution (50 mL) and then filtered and washed with water. The crude product was chromatographed on silica gel with 9:1 CH_2Cl_2–AcOEt as eluant and recrystallized from acetone (175 mL) to yield 4.2 g of **41** (53%), mp 213 °C. Anal. ($C_{17}H_{14}N_3F_3O_2S$), C, H, N, F, S.

Method A1. 4-Hydroxy-2-methyl-8-(trifluoromethyl)-*N*-(2-thiazolyl)-3-quinolinecarboxamide (37). This compound was prepared from ethyl 4-hydroxy-2-methyl-8-(trifluoromethyl)-3-quinolinecarboxylate[14] (6 g, 0.02 mol) and 2-aminothiazole (4 g, 0.04 mol) according to the procedure published earlier.[9]

Method A2. 4-Hydroxy-8-methoxy-*N*-(2-thiazolyl)-3-quinolinecarboxamide (20). (I) 4-Hydroxy-8-methoxy-3-quinolinecarbonyl Chloride. A suspension of 4-hydroxy-8-methoxy-3-quinolinecarboxylic acid[15] (2.2 g, 0.01 mol) in 1,2-dichlorethane (240 mL) and thionyl chloride (0.9 mL, 0.012 mol) was refluxed for 2 h. The resulting slurry was cooled and filtered to yield 2.26 g (95%) of the title compound, mp 258–260 °C. Anal. ($C_{11}H_8ClNO_3$) Cl: calcd, 14.9; found, 14.4.

(II) 4-Hydroxy-8-methoxy-*N*-(2-thiazolyl)-3-quinolinecarboxamide (20). A solution of 2-aminothiazole (0.95 g, 0.0095 mol) in pyridine (15 mL) was added dropwise to a suspension of the product obtained above (2.26 g, 0.0095 mol) in pyridine (5 mL). The mixture was stirred at room temperature overnight. The insoluble product was filtered and washed with ethyl ether. Two recrystallizations from acetic acid gave 2.1 g (64%) of **20**, mp ≥340 °C. Anal. ($C_{14}H_{11}N_3O_3S$) C, H, N, S.

Method B. 2-[(*S*)-1-Aminopropyl]-4-hydroxy-*N*-(2-thiazolyl)-8-(trifluoromethyl)-3-quinolinecarboxamide (118). (I) 1,1-Dimethylethyl [(*S*)-1-[4-Oxo-8-(trifluoromethyl)-4*H*-3,1-benzoxazin-2-yl]propyl]carbamate (4n). To a cooled solution (−20 °C) of Boc-L-α-aminobutyric acid (10.16 g, 0.05 mol) and *N*-methylmorpholine (13.7 mL, 0.125 mol) in methylene chloride was added dropwise a solution of isobutyl chloroformate (13 mL, 0.1 mol) in methylene chloride (50 mL). After 0.5 h, a solution of 2-amino-3-(trifluoromethyl)benzoic acid[16] (10.25 g, 0.05 mol) and *N*-methylmorpholine (5.49 mL) in methylene chloride (100 mL) was added at the same temperature. The mixture was stirred for 20 h at room temperature and then poured into water and extracted with methylene chloride.

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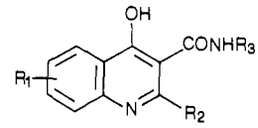
Table V

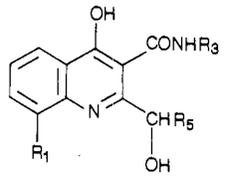


compd	R_1	R_2	R_3	method[a]	yield,[b] %	mp, °C	cryst[c] solv	anal.	acetic acid writhings: ED_{50},[d] mg/kg po	carrageenin edema: ED_{50},[d] mg/kg po
14	H	H	2-thiazolyl	A2	36	>340	AA	C,H,N,S	>10	10
15	8-Cl	H	2-thiazolyl	A2	73	>340	DMF	C,H,N,Cl,S	100	–[e]
16	7-Cl	H	2-thiazolyl	A2	62	>340	DMF	C,H,N,Cl,S	>100	IA 300[f]
17	6-Cl	H	2-thiazolyl	A2	55	>340	AA	C,H,N,Cl,S[g]	50	–
18	8-SCF_3	H	2-thiazolyl	A2	29	304–306	AL	C,H,N,F,S	>50	–
19	8-OCF_3	H	2-thiazolyl	A2	84	303–305	AA	C,H,N,F,S	>50	–
20	8-OCH_3	H	2-thiazolyl	A2	64	>340	AA	C,H,N,S	>50	–
21	6-$CH(CH_3)_2$	H	2-thiazolyl	A2	10	338–340	AA	C,H,N,S	25	–
22	6-CF_3	H	2-thiazolyl	A2	51	>340	AA	C,H,N,F,S	40	–
23	7-CF_3	H	2-thiazolyl	A2	56	>340	DMF	C,H,N,F,S	100	–
24	8-CF_3	H	2-thiazolyl	B	76	>340	AA	C,H,N,F,S	5	>300
25[h]	8-CF_3	H	2-imidazolyl	A2	20	270–272	W	C,H,N,Cl,F	18	25
26	8-CF_3	H	C_6H_5	A2	54	>340	AA	C,H,N,F	>50	–
27	8-CF_3	H	cyclohexyl	A2	74	302–304	AA	C,H,N,F	>50	–
28	8-CF_3	H	2-pyrimidyl	A2	46	320–325	AA	C,H,N,F	50	–
29	8-CF_3	H	2-pyridyl	A2	41	333–335	Aa	C,H,N,F	>50	–
30	8-CF_3	H	3-triazolyl	A2	42	>340	AA	C,H,N,F	>50	–
31[i]	8-CF_3	H	*N*-methyl-2-imidazolyl	A2	72	295–298	AL	C,H,N,Cl,F	16	>100
32	8-CF_3	H	1-methyl-5-pyrazolyl	A2	64	>340	AL	C,H,N,F	50	–
33	8-CF_3	H	2-oxazolyl	A2	51	302–304	M	C,H,N,F	>100	–
34	8-CF_3	H	4,5-dihydro-2-thiazolyl	A2	24	265–267	AL	C,H,N,F,S	15	40
35	8-CF_3	H	5-methyl-3-isoxazolyl	A2	47	302–304	AA	C,H,N,F	IA 50	–
36	8-CF_3	H	5-methyl-2-thiazolyl	A2	48	>340	AA	C,H,N,F,S	IA 50	–
37	8-CF_3	CH_3	2-thiazolyl	A1	93	268–270	AA	C,H,N,F,S	4	>50
38	8-CF_3	CH_2CH_3	2-thiazolyl	A	46	238–240	AA	C,H,N,F,S	3	200
39	8-CF_3	n-C_3H_7	2-thiazolyl	A	41	222–224	AA	C,H,N,F,S	15	–
40	8-CF_3	n-C_4H_9	2-thiazolyl	A	48	180–181	ML	C,H,N,F,S	50	IA 20
41	8-CF_3	$CH(CH_3)_2$	2-thiazolyl	A	53	212–213	AC	C,H,N,F,S	5	–
42	8-CF_3	$CH_2CH(CH_3)_2$	2-thiazolyl	A	32	170–172	ML	C,H,N,F,S	30	–
43	8-CF_3	$C(CH_3)_3$	2-thiazolyl	B	13	222–223	EE	C,H,N,F,S	>100	50
44	8-CF_3	$CH{=}CH_2$	2-thiazolyl	B	55	236–237	A	C,H,N,S	IA 25	IA 25
45	8-CF_3	$CH_2C_6H_5$	2-thiazolyl	A	26	256–257	AA	C,H,N,F,S	40	IA 20
46	8-CF_3	C_6H_5	2-thiazolyl	A	39	238–240	AA	C,H,N,F,S	50	IA 20
47	8-CF_3	CH_3	2-pyridyl	A1	78	191–193	AL	C,H,N,F	5	–
48	8-CF_3	C_2H_5	2-pyridyl	A	64	183–184	ML	C,H,N,F	18	>100
49	8-CF_3	C_2H_5	2-oxazolyl	A	34	211–213	ML	C,H,N,F	15	–
50	8-CF_3	C_2H_5	*N*-methyl-2-imidazolyl	A1	10	208–210	ML	C,H,N,F	50	–
51	8-CF_3	C_2H_5	5-methyl-3-isoxazolyl	A	48	203–204	AE	C,H,N,F	>50	–
52	8-CF_3	$CHCl_2$	2-thiazolyl	B	86	204–205	EA	C,H,N,Cl,F,S	1.1	>100
53	8-CF_3	$CHClCH_3$	2-thiazolyl	B	81	192–193	EE	C,H,N,Cl,S	25	>25
54	8-CF_3	CCl_2CH_3	2-thiazolyl	B	39	220–222	EE	C,H,N,Cl,S	IA 25	25
55	8-CF_3	CH_2Cl	2-thiazolyl	B	64	218–220	THF/PE	C,H,N,Cl,S	25	IA 25
56	8-CF_3	CHF_2	2-thiazolyl	B	67	226–228	EA	C,H,N,F,S	5	5
57	8-CF_3	CF_2CF_3	2-thiazolyl	A2	41	210–211	AA	C,H,N,F,S	20	20
58	8-CF_3	CF_3	2-thiazolyl	A2	23	258–260	MA	C,H,N,F,S	0.5	4.2
59	8-CF_3	$CHCl_2$	*N*-methyl-2-imidazolyl	A1	42	240–242	AL	C,H,N,F,S	>25	IA 25
60	8-CF_3	$CHCl_2$	2-benzothiazolyl	A1	41	266–268	T	C,H,N,Cl,S	>25	IA 25
61	8-CF_3	$CHCl_2$	2-pyridyl	B	39	212–213	EA	C,H,N,Cl,F	20	>100
62	8-CF_3	$CHCl_2$	2-oxazolyl	B	42	220–221	AC	C,H,N,Cl,F	>25	IA 25
63	8-CF_3	CF_3	*N*-methyl-2-imidazolyl	A2	34	259–261	AA	C,H,N,F	IA 100	IA 100
64	8-CF_3	CF_3	2-pyridyl	A2	37	236–238	AA	C,H,N,F	>20	20
65	8-CF_3	CF_3	2-oxazolyl	A2	31	258–261	AA	C,H,N,F	>100	100
66	8-CF_3	CF_3	5-methyl-3-isoxazolyl	A2	49	215–217	AA	C,H,N,F	>50	50
67	6-OCH_3	CF_3	2-thiazolyl	A2	58	266–268	ML	C,H,N,F,S	30	100
68	6-$CH(CH_3)_2$	CF_3	2-thiazolyl	A2	38	262–263	ML	C,H,N,F,S	>100	IA 100
69	7-CF_3	CF_3	2-thiazolyl	A2	38	270–271	AA	C,H,N,F,S	5	5
70	H	CF_3	2-thiazolyl	B	84	270–271	AA	C,H,N,F,S	8	≥100
71	6-Cl	CF_3	2-thiazolyl	B	68	308–310	AL	C,H,N,Cl,F,S	>25	>25
72	7-Cl	CF_3	2-thiazolyl	B	69	303–305	AL	C,H,N,Cl,F,S	>25	>25
73	8-Cl	CF_3	2-thiazolyl	B	88	250–251	AL	C,H,N,Cl,F,S	2	20
74	8-F	CF_3	2-thiazolyl	B	70	240–241	AL	C,H,N,F,S	5	25
75	6-CF_3	CF_3	2-thiazolyl	B	14[j]	280–281	EA	C,H,N,F,S	100	80
76	8-SCF_3	CF_3	2-thiazolyl	B	65[k]	260–262	D	C,H,N,F,S	4	>15
77	8-$SOCF_3$	CF_3	2-thiazolyl	*l*	12	252–254	A	C,H,N,F,S	20	30
78	5-CF_3, 8-Cl	CF_3	2-thiazolyl	B	3	255–257	EE	C,H,N,Cl,S	>50	>50
79[m]	5-CF_3	CF_3	2-thiazolyl	*n*	36	279–281	THF	C,H,N,F,S	20	>20
80	H	$CHCl_2$	2-thiazolyl	B	56	260–262	AA	C,H,N,Cl,S	>25	>25
81[o]	6-Cl	$CHCl_2$	2-thiazolyl	B	78	184–185	AL	C,H,N,Cl,S	25	25
82	8-Cl	$CHCl_2$	2-thiazolyl	B	74	232–233	AL	C,H,N,Cl,S	25	IA 25
83	8-F	$CHCl_2$	2-thiazolyl	B	83	242–243	AL	C,H,N,Cl,S	25	IA 25
84[p]	7-Cl	$CHCl_2$	2-thiazolyl	B	14	225–227	AA	C,H,N,Cl	>100	>100
85	8-CF_3	CH_2OCH_3	2-thiazolyl	B	85	260–262	D	C,H,N,F,S	25	IA 25

Footnotes to Table V

[a] Starting product: A, acid; A1, ethyl ester; A2, acid chloride. [b] Isolated yields. Generally no attempt was made to optimize these yields. [c] Key: A, acetonitrile; AA, acetic acid; AC, acetone; AL, ethyl alcohol; D, dioxane; EA, ethyl acetate; EE, ethyl ether; M, methyl alcohol; ML, 2-methyl propyl alcohol; PE, petroleum ether; T, toluene; W, water. [d] ED_{50}'s obtained from at least three doses. [e] Not tested. [f] IA, inactive. [g] Analysis, calcd/found: C 51.1, 50.8; H 2.7, 2.8; N 13.7, 13.2; Cl 11.6, 11.3; S 10.5, 10.2. [h] Tested as hydrochloride dihydrate salt. [i] Tested as hydrochloride salt. [j] Based on **4b**. [k] Based on **4c**. [l] By oxidation of **76** with hydrogen peroxide in acetic acid. [m] 1 THF complex. [n] By hydrogenolysis of **78**. [o] 0.5 EtOH complex. [p] AcOH salt.

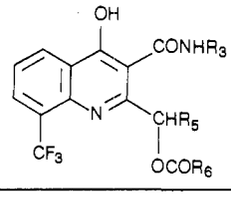
Table VI



compd	R_1	R_5	R_3	yield,[a] %	mp, °C	cryst[b] solv	anal.	adjuvant arthritis: ED_{50},[c] mg/kg po	carrageenin edema: ED_{40},[d] mg/kg po	acetic acid writhings: ED_{50},[c] mg/kg po
86	H	CH_3	2-thiazolyl	35	270–272	DMF/EE	C,H,N,S	>5	4	>100
87	CF_3	H	2-thiazolyl	77[e]	>275	DMF	C,H,N,F,S	IA 25[f]	IA 100	IA 100
88	CF_3	CH_3	2-thiazolyl	57	205–206	EA	C,H,N,F,S	≥5	5	1.2
89	CF_3	C_2H_5	2-thiazolyl	57	204–206	A	C,H,N,F,S	2	5	3
90[g]	CF_3	C_2H_5	2-thiazolyl	77	179–181	EA	C,H,N,F,S	>5	–[h]	>20
91[i]	CF_3	C_2H_5	2-thiazolyl	75	180–182	EA	C,H,N,F,S	0.5	–	1.8
92	CF_3	n-C_3H_7	2-thiazolyl	35	180–182	IS	C,H,N,F,S	≥20	20	20
93	CF_3	$CH(CH_3)_2$	2-thiazolyl	59	219–221	AL	C,H,N,F,S	0.4	4	20
94	CF_3	n-C_4H_9	2-thiazolyl	48	190–191	EA	C,H,N,F,S	>20	>100	≥100
95	CF_3	$C(CH_3)_3$	2-thiazolyl	45	224–226	THF/EE	C,H,N,F,S	1.5	4	50
96	CF_3	cyclohexyl	2-thiazolyl	55	252–254	ML	C,H,N,F,S	IA 10	>100	IA 100
97	CF_3	C_6H_5	2-thiazolyl	70	240–241	A	C,H,N,F,S	IA 10	IA 100	IA 100
98	CF_3	CH_3	2-pyridyl	30	210–212	*j*	C,H,N,F	–	20	>50
99	CF_3	C_2H_5	2-pyridyl	39	220–221	EA	C,H,N,F	≥15	10	20
100	CF_3	$CH(CH_3)_2$	2-pyridyl	59	238–240	EE	C,H,N,F	5	4	>50

[a] Isolated yields. Generally no attempt was made to optimize these yields. [b] Key: A, acetonitrile; AL, ethyl alcohol; EA, ethyl acetate; EE, ethyl ether; ML, 2-methylpropyl alcohol. [c] See footnote *d* in Table V. [d] ED_{40}'s obtained from at least three doses. [e] By treatment of **85** with boron tribromide in methylene dichloride. [f] IA, inactive. [g] $[\alpha]^{20}_D$ +54° (*c* 0.5, acetone). [h] Not tested. [i] $[\alpha]^{20}_D$ –52° (*c* 0.5, acetone). [j] Purified by column chromatography on silica gel: methyl alcohol–methylene chloride.

Table VII



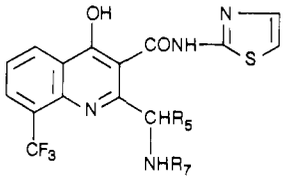
compd	R_5	R_6	R_3	method	yield,[a] %	mp, °C	cryst[b] solv	anal.	adjuvant arthritis: ED_{50},[c] mg/kg po	carrageenin edema: ED_{40},[d] mg/kg po	acetic acid writhings: ED_{50},[c] mg/kg po
101	C_2H_5	CH_3	2-thiazolyl	C	62	246–247	EA	C,H,N,F,S	4	100	IA 100[e]
102	C_2H_5	C_2H_5	2-thiazolyl	C	70	214–216	EA	C,H,N,F,S	0.7	4	50
103[f]	C_2H_5	C_2H_5	2-thiazolyl	D	68	187–188	EA	C,H,N,F,S	>5	*g*	>50
104[h]	C_2H_5	C_2H_5	2-thiazolyl	D	63	187–189	EA	C,H,N,F,S	0.6	–	15
105	C_2H_5	n-C_3H_7	2-thiazolyl	D	83	201–204	EA	C,H,N,F,S	1.3	20	4
106	C_2H_5	$C(CH_3)_3$	2-thiazolyl	D	85	244–246	EA	C,H,N,F,S	15	–	–
107	C_2H_5	n-$C_{11}H_{23}$	2-thiazolyl	D	82	158–160	EA	C,H,N,F,S	>5	–	IA 100
108	C_2H_5	$C_6H_5CH{=}CH$	2-thiazolyl	D	70	210–211	A	C,H,N,F,S	10	–	>100
109	C_2H_5	C_6H_5	2-thiazolyl	D	74	230–232	EA	C,H,N,F,S	>5	–	>100
110	C_2H_5	3-pyridyl	2-thiazolyl	D	75	200–201	EA	C,H,N,F,S	>1	–	>20
111	C_2H_5	C_2H_5	2-pyridyl	D	43	204–205	EA	C,H,N,F	>5	–	IA 100
112	$CH(CH_3)_2$	CH_3	2-thiazolyl	C	46	242–243	EA	C,H,N,F,S	≥5	10	>100
113	$CH(CH_3)_2$	C_2H_5	2-thiazolyl	C	46	222–225	EA	C,H,N,F,S	≥5	10	>100
114	$CH(CH_3)_2$	CH_3	2-pyridyl	C	51	230–231	EA	C,H,N,F	>5	–	IA 100
115	$CH(CH_3)_2$	C_2H_5	2-pyridyl	C	38	192–193	EA	C,H,N,F	5	–	IA 100

[a] Isolated yields. Generally no attempt was made to optimize these yields. [b] Key: A, acetonitrile; EA, ethyl acetate. [c] See footnote *d* in Table V. [d] See footnote *d* in Table VI. [e] IA, inactive. [f] $[\alpha]^{20}_D$ –9.5° (*c* 0.5, acetone). [g] Not tested. [h] $[\alpha]^{20}_D$ +8.5° (*c* 0.5, acetone).

The combined organic layers were dried and evaporated to afford 9.9 g (53%) of **4n**, mp 136–38 °C; $[\alpha]^{20}_D$ –68° (c 1, CH_3COOH). Anal. ($C_{17}H_{19}F_3N_2O_4$) C, H, N, F, S.

(II) 1,1-Dimethylethyl [(*S*)-2-[[2-[1,3-Dioxo-3-(2-thiazolylamino)propyl]-6-(trifluoromethyl)phenyl]amino]-1-ethyl-2-oxoethyl]carbamate (6l). A solution of butyllithium (78.3 mL, 0.109 mol) in hexane was slowly added to a cold (0 °C) solution of 2-(acetylamino)thiazole (7.78 g, 0.054 mol) in tetrahydrofuran (240 mL). After the mixture was cooled to –75 °C, a solution of **4n** (10.2 g, 0.027 mol) in tetrahydrofuran 75 mL)

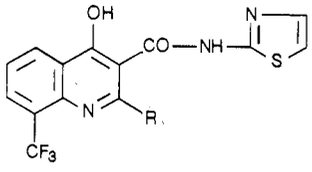
Table VIII



compd	C[a]	R_5	R_7	yield, %	$[\alpha]^{20}_D$, deg	mp, °C	cryst[b] solv	anal.	adjuvant arthritis: ED_{50},[c] mg/kg po	carrageenin edema: ED_{40},[d] mg/kg po	acetic acid writhings: ED_{50},[c] mg/kg po
116	*S*	CH_3	H	72	+62[e]	269–271	M	C,H,N,F,S	7	10	30
117	*R*	CH_3	H	72	−72[e]	265–266	M	C,H,N,F,S	IA 15[f]	IA 100	>100
118	*S*	C_2H_5	H	62	+117[g]	206–208	A	C,H,N,F,S	5	10	35
119	*S*	C_2H_5	$C(O)CH_3$	80	+43[g]	>275	THF	C,H,N,F,S	1.5	35	5
120	*S*	C_2H_5	$C(O)C_2H_5$	82	+57[e]	>275	EE	C,H,N,F,S	3	>100	20
121	*S*	$CH(CH_3)_2$	H	98	−26[h]	163–166[i]	EE	C,H,N,F,S	≥5	≥100	>100

[a] Absolute configuration. [b] Key: A, acetonitrile; EE, ethyl ether; M, methyl alcohol. [c] See footnote *d* in Table V. [d] See footnote *d* in Table VI. [e] (*c* 1, CH_3COOH). [f] IA, inactive. [g] (*c* 1, dimethylformamide). [h] (c 1, ethyl alcohol). [i] Tested as CF_3COOH salt.

Table IX



compd	R	cyclo-oxygenase: IC_{50}, 10^{-6} M	5-lip-oxygenase:[a] IC_{50}, 10^{-6} M	adjuvant arthritis: ED_{50}, mg/kg po	carragee-nin edema: ED_{40},[b] mg/kg po	acetic acid writhings: ED_{50}, mg/kg po	gastric ulcer: ED_{100},[c] mg/kg po	intestinal ulcer: ED_{100},[c] mg/kg po
24	H	2.8 (2.3–3.3)	35 (18–60)	IA 50[d]	>100	5 (3.2–7.9)	>500	IA 500
52	$CHCl_2$	1.8 (1.7–1.9)	2 (0.7–5.9)	48 (29–157)	>100	1.1 (0.7–2.0)	270	>500
58	CF_3	0.4 (0.3–0.6)	3.0 (1.4–6.2)	3.8 (2.0–7.0)	3.5	0.5 (0.1–1.1)	15	–
89	$CHOHC_2H_5$	0.2 (0.2–0.4)	1.1 (0.3–2.4)	1.6 (0.8–6.6)	5	3.0 (1.5–10.4)	12	–
102	$CH(OCOC_2H_5)C_2H_5$	2.1 (0.2–4.3)	3.0 (1.8–5.0)	0.7 (0.3–2.4)	4	4.6[e] (1.5–13.9)	>300	>250
118	$CH(NH_2)C_2H_5$	1.4 (0.7–2.4)	18 (3.8–80)	3.1 (1.9–5.3)	10	30[e]	80	>100
120	$CH(NHCOC_2H_5)C_2H_5$	0.4 (0.3–0.5)	2.0 (1.4–2.7)	3.5 (1.8–6.8)	>100	4[e]	>300	>100
piroxicam		65 (63–68)	>100	0.8 (0.5–1.2)	8 (4–14)	3.3 (2.1–7.0)	9	20

[a] IC_{50} of BW755c is 12 (7–21) micromoles; see ref 14. [b] ED_{40}'s evaluated or calculated from at least four doses. [c] ED_{100} generated from at least four doses. [d] IA, inactive. [e] Treatment 6 h before testing.

was added. The cold reaction mixture was poured into water (400 mL) and 1 N hydrochloric acid (150 mL). The aqueous mixture was extracted with ethyl ether. The combined extracts were dried and evaporated under reduced pressure. Crystallization from methylene chloride yielded 8.3 g of **61** (59%), mp 190 °C; $[\alpha]^{20}_D$ −36.5° (*c* 0.5, CH_3COOH).

(III) 1,1-Dimethyl [(*S*)-1-[4-Hydroxy-3-[(2-Thiazolylamino)carbonyl]-8-(trifluoromethyl)-2-quinolinyl]propyl]carbamate (11c). A mixture of **61** (8 g, 0.015 mol) and 4-(dimethylamino)pyridine (1.9 g, 0.015 mol) in tetrahydrofuran (80 mL) was stirred for 23 h at room temperature. The solution was poured into water and extracted with a mixture of ethyl acetate (400 mL) and tetrahydrofuran (300 mL). The extract was washed with water, dried, and evaporated in vacuo. Crystallization of the residue from ethyl ether gave 6.8 g (88%) of **11c**, mp 260–262 °C; $[\alpha]^{20}_D$ +66.5° (*c* 0.7, CH_3COOH). Anal. ($C_{22}H_{23}F_3O_4N_4S$) C, H, N, F, S.

(IV) 2-[(*S*)-1-Aminopropyl]-4-hydroxy-*N*-(2-thiazolyl)-8-(trifluoromethyl)-3-quinolinecarboxamide (118). A solution of **11c** (6.5 g, 0.013 mol) in trifluoroacetic acid (65 mL) and methylene chloride (130 mL) was stirred at room temperature for 2 h. The solution was concentrated in vacuo and the residue was triturated with water and neutralized (pH 7) with a saturated sodium hydrogen carbonate solution. The solid product was isolated by filtration, washed with water, and dried. Crystallization from acetonitrile gave 3.25 g (62%) of 118, mp 206 °C; $[\alpha]^{20}_D$ +117° (*c* 0.8, CH_3COOH). Anal. ($C_{17}H_{15}F_3N_4O_2S$) C, H, N, F, S.

4-Hydroxy-2-[(*S*)-1-[(1-Oxopropyl)amino]propyl]-*N*-(2-thiazolyl)-8-(trifluoromethyl)-3-quinolinecarboxamide (120). Propionic anhydride (6 mL) was added dropwise to a solution of 118 (3.2 g, 0.008 mol) in pyridine (32 mL). The resulting suspension was poured in water (200 mL) and concentrated hydrochloric acid (26 mL). The precipitate was filtered, washed with water, dried, and crystallized from ethyl ether to give 3 g (82%) of **120**, mp 275 °C; $[\alpha]^{20}_D$ +57° (*c* 0.5, CH_3COOH). Anal. ($C_{20}H_{19}N_3F_3O_3S$) C, H, N, F, S.

4-Hydroxy-2-(1-hydroxy-2-methylpropyl)-*N*-(2-thiazolyl)-8-(trifluoromethyl)-3-quinolinecarboxamide (93). (I) 1,3-Dihydro-3-(1-methylethyl)-1-[(2-thiazolyl)imino]-5-(trifluoromethyl)furo[3,4-*b*]quinolin-9-ol (8d). A solution of **6e**

(11.65 g, 0.026 mol), prepared following the procedure previously described,[9] and 4-(dimethylamino)pyridine (3.8 g, 0.031 mol) in tetrahydrofuran (200 mL) was refluxed for 16 h. The solvent was removed in vacuo, and the residue was triturated with water (200 mL) and acidified with dilute hydrochloric acid. The yellow product was filtered and washed with water to yield 10.2 g (100%) of crude **8d**, mp 248 °C.

(II) 4-Hydroxy-2-(1-hydroxy-2-methylpropyl)-*N*-(2-thiazolyl)-8-(trifluoromethyl)-3-quinolinecarboxamide (93). A mixture of **8d** (10.2 g, 0.030 mol), concentrated hydrochloric acid (100 mL), and water (100 mL) was stirred for 1.5 h at 100 °C. The cooled reaction mixture was filtered and washed with water. The precipitate was dissolved in a mixture of ethyl acetate (200 mL) and water (200 mL). The organic layer was dried and evaporated and the residue was recrystallized from ethyl alcohol to give 6.6 g of **93** (59%), mp 220 °C. Anal. ($C_{18}H_{16}N_3F_3O_3S$) C, H, N, F, S.

Method C. 2-[1-(Acetyloxy)-2-methylpropyl]-4-hydroxy-*N*-(2-thiazolyl)-8-(trifluoromethyl)-3-quinolinecarboxamide (112). A solution of **8d** (10 g, 0.025 mol) in acetic acid (200 mL) was refluxed for 57 h. Water (200 mL) was poured into the cooled reaction, and the precipitate was filtered, washed with water, and dissolved in ethyl acetate (250 mL) and tetrahydrofuran (500 mL). The organic layer was dried and concentrated in vacuo. Recrystallization from ethyl acetate gave 5.3 g (46%) of **112**. Anal. ($C_{20}H_{18}F_3N_3O_4S$) C, H, N, F, S.

Method D. 4-Hydroxy-2-[1-(1-oxobutoxy)propyl]-*N*-(2-thiazolyl)-8-(trifluoromethyl)-3-quinolinecarboxamide (105). To a suspension of **89** (8 g, 0.02 mol), prepared in the same manner as described above for **93**, in methylene chloride (80 mL) were added butyric acid (2 mL, 0.02 mol), dicyclohexylcarbodiimide (4.95 g, 0.024 mol), and, after 5 min, 4-(dimethylamino)pyridine (1.22 g, 0.02 mol). The reaction mixture was stirred at room temperature for 2 h, filtered, and washed with 1 N hydrochloric acid (100 mL), saturated sodium hydrogen carbonate solution (100 mL), and water (100 mL). The organic layer was dried and evaporated to give a residue, which was crystallized in ethyl acetate (150 mL) to afford **105** 9.3 g (83%), mp 203 °C. Anal. ($C_{21}H_{20}N_3F_3O_4S$) C, H, N, F, S.

Resolution of 4-Hydroxy-2-(1-hydroxypropyl)-*N*-(2-thiazolyl)-8-(trifluoromethyl)-3-quinolinecarboxamide (89). (I) Preparation of Diastereoisomeric Esters 89a and 89b. 1-[4-Hydroxy-3-[[(2-thiazolyl)amino]carbonyl]-8-(trifluoromethyl)-2-quinolinyl]propyl (*R*)-α-Methoxybenzeneacetate. Esterification of **89** (28.7 g, 0.072 mol), as described for **105** (method D), with (*R*)-α-methoxyphenylacetic acid (12 g, 0.072 mol) afforded a mixture of **89a** and **89b**. The residue was chromatographed on a column containing silica gel (1.5 kg), with 50% hexane–ethyl acetate as eluent.

The first fraction gave **89a** (15.18 g, 38%), mp 172 °C; $[\alpha]^{20}_D$ −7° (c 0.5, acetone). Anal. ($C_{26}H_{22}N_3F_3O_5S$) C, H, N, F, S.

The second fraction gave **89b** (14.24 g, 36%), mp 194 °C, $[\alpha]^{20}_D$ −30.5° (c 0.5, acetone). Anal. $C_{26}H_{22}N_3F_3O_5S$) C, H, N, F, S.

(II) (+)-4-Hydroxy-2-(1-hydroxypropyl)-*N*-(2-thiazolyl)-8-(trifluoromethyl)-3-quinolinecarboxamide (90). A solution of **89a** (13.68 g, 0.025 mol) in *n*-butylamine (70 mL) was stirred for 24 h at room temperature. Ethyl acetate (500 mL) was added, and the organic layer was washed with 2 N hydrochloric acid and water. The solution was dried and concentrated in vacuo. Crystallization from ethyl acetate gave **90** (3.61 g), mp 180 °C; a second crop of the same product was obtained by chromatography on a silica column with ethyl acetate–methylene chloride (2:8) as eluent (4.03 g): mp 180 °C; yield 77%; $[\alpha]^{20}_D$ +54° (c 0.5, acetone). Anal. ($C_{17}H_{14}N_3F_3O_3S$) C, H, N, F, S.

(III) (−)-4-Hydroxy-2-(1-hydroxypropyl)-*N*-(2-thiazolyl)-8-(trifluoromethyl)-3-quinolinecarboxamide (91). By a similar procedure **91** was obtained from **89b** (13.68 g): yield 75% (7.4 g); mp 180 °C; $[\alpha]^{20}_D$ −52° (c 0.5, acetone). Anal. ($C_{17}H_{14}N_3F_3O_3S$) C, H, N, F, S.

Pharmacology. Determination of Cyclooxygenase Activity. Microsomes were prepared from bovine seminal vesicles according to the method described by Takeguchi et al.[17] The reaction mixture contained 1.8 mg/mL of microsomal protein, arachidonic acid (15×10^{-6} M), and test compounds in 2 mL of 0.05 M Tris buffer, pH 7.4. After incubation for 30 min at 37 °C, the reaction was stopped by heating; then PGE_2 and $PGF_{2\alpha}$ were assayed by radioimmunoassay. Assays were performed at least in duplicate. IC_{50}'s were calculated from at least five concentrations by means of a computerized least-squares curve-fitting procedure.

Determination of 5-Lipoxygenase Activity. Casein elicited rat peritoneal neutrophils (5×10^6 cells/mL) were preincubated with test compounds for 5 min at 37 °C; ionophore A23187 and calcium chloride were then added at 10 μM and 5 mM, respectively. After a further 5 min incubation at 37 °C, the tubes were cooled on ice and the cells centrifuged at 800*g*. Leucotriene B_4 (LTB_4) was assayed in the supernatant by radioimmunoassay. Assays were performed at least in duplicate. IC_{50}'s were calculated from at least four concentrations by using a computerized least-squares curve-fitting procedure.

Carrageenin-Induced Foot Edema. Groups of eight male rats (Sprague–Dawley, 150–180 g) were dosed orally simultaneously with the subplantar injection of 0.5 mg of carrageenin according to the method of Winter et al.[18]

Inflammation was assessed as the difference in volume before and 5 h after the injection of the phlogogenic agent. ED_{50}'s were either estimated graphically or calculated by a probit analysis according to Litchfield and Wilcoxon.[19] Results in Tables VI–IX are expressed as the ED_{40} value because the effects often plateau at 40° of inhibition.

Adjuvant-Induced Arthritis. The method used derived from that described by Walz et al.[20] Groups of five male Lewis rats, 40–50 days old, were given an intraplantar injection into the right hind paw of 0.6 mg of *Mycobacterium butyricum* homogenized in 0.1 mL of Bayol 55. The volume of injected and noninjected hind paws were measured on day 17 when the secondary lesions were fully developed. Drugs were administered in the food from the day of the injection of the adjuvant until day 17.

The criteria for evaluation of the drugs' activity were as follows: (a) the increase in the volume of the injected hind paw (primary and later, secondary inflammations) and the noninjected hind paw (secondary inflammation) compared with the mean volume of the corresponding paws of the normal controls, (b) the growth rate, (c) the arthritis of the forepaws rated from 0 to 3 according to the intensity of the inflammations, (d) the inflammation of the ears and nodes in the tail rated 1 or 0 (present or absent), and (e) the serum level of α_2-macroglobulin[21] determined by immunological titration.

Data presented here only considered the effect of drugs on the inflammations of hind paws; ED_{50}'s were obtained either with use of a computerized least-squares curve-fitting procedure or by means of probit analysis according to Litchfield and Wilcoxon (Table IX).

Acetic Acid Induced Writhings. Writhings were induced in groups of 10 female mice (20–22 g) fasted for 7 h according to the method described by Koster et al.[22] Test drugs were administered by the oral route 30 min before the intraperitoneal injection of 0.2 mL of 1% acetic acid aqueous solution. Stretching and writhing movements were counted from the 5th to the 20th minute after the irritant injection. ED_{50}'s were either evaluated graphically or calculated by means of a computerized least-squares curve-fitting procedure.

Ulcerogenic Effect. The tests used were those described by Peterfalvi et al.[23]

Fasted Rats. Compounds were administered orally to groups of eight female rats (120–150 g) fasted for 24 h. Animals were sacrificed 7 h after the treatment, and the stomachs were removed,

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cut along the greater curvature, put in 9% NaCl, and checked for petechial hemorrhages and ulcers. On a blind analysis, the extent of the lesions, taking into account their number, was rated on a scale from 0 to 3. An index of ulceration was calculated as indicated below, taking into account the percentage of animals having ulcers (stomachs rated above 0.5, a score corresponding to hyperemia or petechiae, often found in fasted rats):

$$\text{index} = (\text{mean degree of ulcer} \times \text{number of rats with ulcers/number of rats}) \times 100$$

The ED_{100}, which corresponds to an index of 100 (maximal score of 300), was determined graphically.

Nonfasted Rats. Male rats (150–180 g) were killed 24 h after oral administration of test compounds. Intestinal ulcers were noted as previously described, and the ED_{100} was calculated according to the same procedure.

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Registry No. **2** (R_1 = H, R_2 = H, R_4 = Cl), 64321-68-2; **2** (R_1 = 8-Cl, R_2 = H, R_4 = Cl), 59197-88-5; **2** (R_1 = 7-Cl, R_2 = H, R_4 = Cl), 59197-91-0; **2** (R_1 = 6-Cl, R_2 = H, R_4 = Cl), 114351-49-4; **2** (R_1 = 8-SCF_3, R_2 = H, R_4 = Cl), 66757-44-6; **2** (R_1 = 8-OCF_3, R_2 = H, R_4 = Cl), 66757-45-7; **2** (R_1 = 8-OCH_3, R_2 = H, R_4 = Cl), 114351-50-7; **2** (R_1 = 6-$CH(CH_3)_2$, R_2 = H, R_4 = Cl), 64356-15-6; **2** (R_1 = 6-CF_3, R_2 = H, R_4 = Cl), 114351-51-8; **2** (R_1 = 7-CF_3, R_2 = H, R_4 = Cl), 59197-90-9; **2** (R_1 = 8-CF_3, R_2 = H, R_4 = Cl), 59197-85-2; **2** (R_1 = 8-CF_3, R_2 = CH_3, R_4 = OC_2H_5), 64321-66-0; **2** (R_1 = 8-CF_3, R_2 = C_2H_5, R_4 = OH), 64321-70-6; **2** (R_1 = 8-CF_3, R_2 = *n*-C_3H_7, R_4 = OH), 64321-80-8; **2** (R_1 = 8-CF_3, R_2 = *n*-C_4H_9, R_4 = OH), 64321-85-3; **2** (R_1 = 8-CF_3, R_2 = $CH(CH_3)_2$, R_4 = OH), 64321-75-1; **2** (R_1 = 8-CF_3, R_2 = $CH_2CH(CH_3)_2$, R_4 = OH), 64321-90-0; **2** (R_1 = 8-CF_3, R_2 = $CH_2C_6H_5$, R_4 = OH), 64322-02-7; **2** (R_1 = 8-CF_3, R_2 = C_6H_5, R_4 = OH), 64321-97-7; **2** (R_1 = 8-CF_3, R_2 = C_2H_5, R_4 = OC_2H_5), 64321-74-0; **2** (R_1 = 8-CF_3, R_2 = CF_2CF_3, R_4 = Cl), 114351-52-9; **2** (R_1 = 8-CF_3, R_2 = CF_3, R_4 = Cl), 75999-37-0; **2** (R_1 = 8-CF_3, R_2 = $CHCl_2$, R_4 = OC_2H_5), 80777-17-9; **2** (R_1 = 6-OCH_3, R_2 = CF_3, R_4 = Cl), 75999-51-8; **2** (R_1 = 6-$CH(CH_3)_2$, R_2 = CF_3, R_4 = Cl), 75999-49-4; **2** (R_1 = 7-CF_3, R_2 = CF_3, R_4 = Cl), 75999-45-0; **3** (R_1 = H), 118-92-3; **3** (R_1 = 5-CF_3), 83265-53-6; **3** (R_1 = 3-SCF_3), 114351-53-0; **3** (R_1 = 4-Cl), 89-77-0; **3** (R_1 = 3-CF_3), 313-12-2; **4a**, 114351-16-5; **4b**, 114351-17-6; **4c**, 114351-18-7; **4d**, 114351-19-8; **4e**, 114351-20-1; **4f**, 114351-21-2; **4g**, 114351-22-3; **4h**, 114351-23-4; **4i**, 114351-24-5; **4j**, 114351-25-6; **4k**, 114351-26-7; **4l**, 105100-67-2; 4m, 105100-66-1; **4n**, 105100-69-4; **4o**, 105100-71-8; 4 (R_1 = 8-CF_3, R_2 = $CHClCH_3$), 114351-54-1; **6a**, 114351-27-8; **6b**, 114351-28-9; **6c**, 114351-29-0; **6d**, 114351-30-3; **6e**, 114377-09-2; **6f**, 114351-31-4; **6g**, 114351-32-5; **6h**, 114351-33-6; **6i**, 114351-34-7; **6j**, 105100-68-3; **6k**, 105100-78-5; **6l**, 105100-70-7; **6m**, 105100-79-6; **6n**, 114351-35-8; **6o**, 114351-36-9; **6p**, 114351-37-0; **6** (R_1 = 3-CF_3, R_2 = H, R_3 = 2-thiazolyl), 95632-32-9; **6** (R_1 = 3-CF_3, R_2 = $C(CH_3)_3$, R_3 = 2-thiazolyl), 95632-36-3; **6** (R_1 = 3-CF_3, R_2 = [$CH{=}CH_2$], R_3 = 2-thiazolyl), 95632-35-2; **6** (R_1 = 3-CF_3, R_2 = $CHCl_2$, R_3 = 2-thiazolyl), 80777-36-2; **6** (R_1 = 3-CF_3, R_2 = $CHClCH_3$, R_3 = 2-thiazolyl), 114351-57-4; **6** (R_1 = 3-CF_3, R_2 = CCl_2CH_3, R_3 = 2-thiazolyl), 80777-41-9; **6** (R_1 = 3-CF_3, R_2 = CH_2Cl, R_3 = 2-thiazolyl), 80777-37-3; **6** (R_1 = 3-CF_3, R_2 = CHF_2, R_3 = 2-thiazolyl), 80777-43-1; **6** (R_1 = 3-CF_3, R_2 = $CHCl_2$, R_3 = 2-pyridyl), 114351-58-5; **6** (R_1 = 3-CF_3, R_2 = $CHCl_2$, R_3 = 2-oxazolyl), 80777-45-3; **6** (R_1 = H, R_2 = CF_3, R_3 = 2-thiazolyl), 95632-06-7; **6** (R_1 = 5-Cl, R_2 = CF_3, R_3 = 2-thiazolyl), 91457-76-0; **6** (R_1 = 4-Cl, R_2 = CF_3, R_3 = 2-thiazolyl), 91457-73-7; **6** (R_1 = 3-Cl, R_2 = CF_3, R_3 = 2-thiazolyl), 91457-68-0; **6** (R_1 = 3-F, R_2 = CF_3, R_3 = 2-thiazolyl), 91457-71-5; **6** (R_1 = [6-CF_3, 3-Cl], R_2 = CF_3, R_3 = 2-thiazolyl), 114351-59-6; **6** (R_1 = H, R_2 = $CHCl_2$, R_3 = 2-thiazolyl), 95632-38-5; **6** (R_1 = 5-Cl, R_2 = $CHCl_2$, R_3 = 2-thiazolyl), 95632-02-3; **6** (R_1 = 3-Cl, R_2 = $CHCl_2$, R_3 = 2-thiazolyl), 95632-03-4; **6** (R_1 = 3-F, R_2 = $CHCl_2$, R_3 = 2-thiazolyl), 95632-04-5; **6** (R_1 = 3-CF_3, R_2 = CH_2OCH_3, R_3 = 2-thiazolyl), 89467-07-2; **8a**, 114351-38-1; **8b**, 114351-39-2; **8c**, 114351-40-5; **8d**, 114351-41-6; **8e**, 114351-42-7; **8f**, 114351-43-8; **8g**, 114351-44-9; **8h**, 114351-45-0; **8i**, 114351-46-1; **8j**, 114351-47-2; **8k**, 114351-48-3; **11a**, 105100-53-6; **11b**, 105100-51-4; **11c**, 105100-55-8; **11d**, 105100-57-0; **14**, 64321-69-3; **15**, 59197-89-6; **16**, 65246-67-5; **17**, 114350-65-1; **18**, 66757-46-8; **19**, 66757-47-9; **20**, 114350-66-2; **21**, 64321-59-1; **22**, 114350-67-3; **23**, 59197-94-3; **24**, 59197-86-3; **25**, 64321-57-9; **25**·HCl, 64321-58-0; **26**, 114350-68-4; **27**, 114350-69-5; **28**, 114350-70-8; **29**, 59197-87-4; **30**, 114350-71-9; **31**, 114350-72-0; **31**·HCl, 114350-62-8; **32**, 114350-73-1; **33**, 59197-93-2; **34**, 64321-56-8; **35**, 114350-74-2; **36**, 114350-75-3; **37**, 64321-64-8; **38**, 64321-71-7; **39**, 64321-81-9; **40**, 64321-86-4; 41, 64321-76-2; **42**, 64321-91-1; **43**, 95632-08-9; 44, 95632-07-8; **45**, 64322-03-8; **46**, 64321-98-8; **47**, 114350-76-4; **48**, 114350-77-5; **49**, 114350-78-6; **50**, 114350-79-7; **51**, 114350-80-0; **52**, 80777-20-4; **53**, 114350-81-1; **54**, 80777-34-0; **55**, 80783-80-8; **56**, 80777-44-2; **57**, 114350-82-2; **58**, 75999-36-9; **59**, 80777-33-9; **60**, 80777-28-2; **61**, 80777-22-6; **62**, 80777-32-8; **63**, 75999-41-6; **64**, 75999-40-5; **65**, 75999-38-1; **66**, 75999-39-2; **67**, 75999-50-7; **68**, 75999-46-1; **69**, 75999-44-9; **70**, 75999-47-2; **71**, 91457-77-1; **72**, 91457-74-8; **73**, 91457-69-1; **74**, 91457-72-6; **75**, 114350-83-3; **76**, 114350-84-4; **77**, 114350-85-5; **78**, 114350-86-6; **79**, 114350-63-9; **80**, 95632-10-3; **81**, 95632-11-4; **82**, 95632-12-5; **83**, 95632-13-6; **84**, 114350-64-0; **84**·AcOH, 114350-87-7; **85**, 89441-10-1; **86**, 114350-88-8; **87**, 89441-32-7; **88**, 114377-08-1; **89**, 114350-89-9; **89a**, 114351-55-2; **89b**, 114351-56-3; **90**, 114419-80-6; **91**, 114419-81-7; **92**, 114350-90-2; **93**, 114350-91-3; **94**, 114350-92-4; **95**, 114350-93-5; **96**, 114350-94-6; **97**, 114350-95-7; **98**, 114350-96-8; **99**, 114350-97-9; **100**, 114350-98-0; **101**, 114350-99-1; **102**, 114351-00-7; **103**, 114351-01-8; **104**, 114351-02-9; **105**, 114351-03-0; **106**, 114351-04-1; **107**, 114351-05-2; **108**, 114351-06-3; **109**, 114351-07-4; **110**, 114351-08-5; 111, 114351-09-6; **112**, 114351-10-9; **113**, 114351-11-0; 114, 114351-12-1; **115**, 114351-13-2; **116**, 105100-54-7; **117**, 105100-52-5; **118**, 105100-56-9; **119**, 114351-14-3; **120**, 114351-15-4; **121**, 105100-58-1; **121**·CF_3CO_2H, 105100-59-2; (*R*)-$HO_2CCH(OCH_3)C_6H_5$, 3966-32-3; $HO_2CCHClCH_3$, 62138-52-7; HO_2CCF_3, 76-05-1; HO_2CCHCl_2, 79-43-6; $HO_2CCHClC_2H_5$, 600-12-4; $HO_2CCHCl(CH_2)_2CH_3$, 94347-45-2; $HO_2CCHClCH(CH_3)_2$, 91423-85-7; $HO_2CCHCl(CH_2)_3CH_3$, 114419-82-8; $HO_2CCHClC(CH_3)_3$, 80845-21-2; $HO_iCCHCl\text{-}c\text{-}C_6H_{11}$, 114377-10-5; $HO_2CCHClC_6H_5$, 39266-56-3; (*S*)-$HO_2CCH(NHBoc)CH_3$, 15761-38-3; (*R*)-$HO_2CCH(NHBoc)CH_3$, 7764-95-6; (*S*)-$HO_2CCH(NHBoc)CH(CH_3)_2$, 13734-41-3; $H_2NC_6H_5$, 62-53-3; AcOH, 64-19-7; $C_2H_5CO_2H$, 79-09-4; n-$C_3H_7CO_2H$, 107-92-6; $C(CH_3)_3CO_2H$, 75-98-9; n-$C_{11}H_{23}CO_2H$, 143-07-7; $C_6H_5CH{=}CHCO_2H$, 621-82-9; $C_6H_5CO_2H$, 65-85-0; 4-hydroxy-8-methoxy-3-quinolinecarboxylic acid, 28027-18-1; Boc-L-α-aminobutyric acid, 34306-42-8; 2-(acetylamino)thiazole, 2719-23-5; 2-(acetylamino)pyridine, 5231-96-9; 2-aminothiazole, 96-50-4; 2-aminoimidazole, 7720-39-0; aminocyclohexane, 108-91-8; 2-aminopyrimidine, 109-12-6; 2-aminopyridine, 504-29-0; 3-aminotriazole, 61-82-5; 2-amino-*N*-methylimidazole, 6646-51-1; 5-amino-1-methylpyrazole, 1192-21-8; 2-aminooxazole, 4570-45-0; 2-amino-4,5-dihydrothiazole, 1779-81-3; 3-amino-5-methylisoxazole, 1072-67-9; 2-amino-5-methylthiazole, 7305-71-7; 2-aminobenzothiazole, 136-95-8; 3-pyridinecarboxylic acid, 59-67-6.