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Structure–Activity Relationships in a Series of 3-Sulfonylamino-2-(1*H*)-Quinolones, as new AMPA/Kainate and Glycine Antagonists

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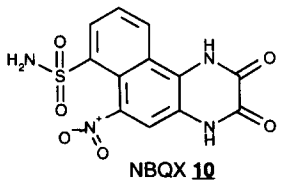
Abstract—This paper describes the design and synthesis of a new class of molecules, the 3-sulfonylamino-2-(1*H*)-quinolones, which are potent and selective antagonists at both the AMPA/kainate site as well as at the NMDA-associated glycine site. The molecules were characterized by their binding affinities to rat cortical membranes and by electrophysiology on *Xenopus* oocytes injected with mRNA isolated from rat cerebral cortex. The most potent compound **61** has an IC_{50} of 0.09 μM for binding at the AMPA/kainate site, and 0.16 μM in oocyte electrophysiology.

Introduction

L-Glutamic acid is the predominant excitatory neurotransmitter in the mammalian central nervous system.[1] Various receptors for glutamic acid have been characterized;[2] some were shown to be ion channels, whilst others were found to act through G protein coupled second messenger systems. Pharmacologically, the best defined receptors are the ion channels activated either by *N*-methyl-D-aspartic acid (NMDA) or by α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainic acid. These two receptors have been implicated in neuronal excitotoxicity following ischaemic insult (stroke)[3] or epileptic seizures.[4]

In recent years, intense research efforts have been devoted to the discovery of antagonists of these receptors and various NMDA antagonists are presently in clinical trials. The co-agonist role of glycine on this receptor was discovered in 1987[5] and pharmacological manipulation of NMDA transmission has been attempted through the search for agonists[6] and antagonists[7] at this site.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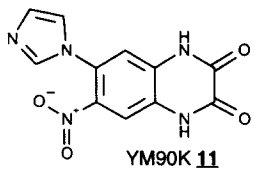
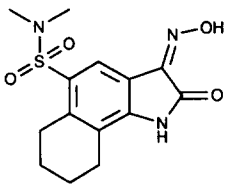
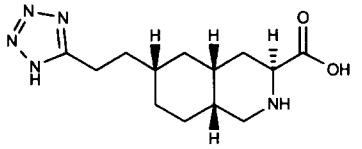
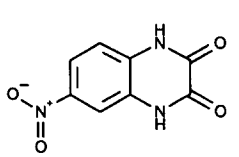

YM90K **11**


NS 229 **12**


LY 293558 **13**


6-NQX **14**

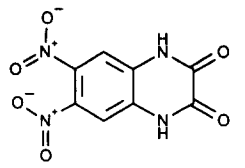

DNQX **15**

Figure 1.

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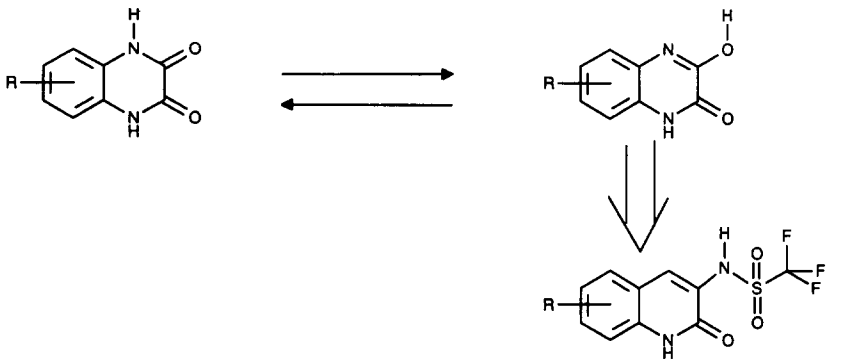


Figure 2.

Selective AMPA/kainate antagonists belong either to the acidic heterocycle class (NBQX[8] **10**, YM90K[9] **11** and NS 229[10] **12**, Fig. 1) or to the amino acid class (LY 293558[11] **13**, Fig. 1). In addition, several quinoxalinediones are non-selective AMPA/glycine antagonists (6-NQX **14** and DNQX[12] **15**, Fig. 1). More recently, scientists at Merck disclosed a series of 3-nitro-3,4-dihydro-2(1*H*)-quinolones as potent combined AMPA–glycine/NMDA antagonists[13] and a group at Parke–Davis reported *N*-sulfonyl derivatives of 3,4-dihydro-3-oxo-quinoxaline carboxylate as NMDA-associated glycine and AMPA antagonists.[14]

At the time we started our search for excitatory amino acid (EAA) antagonists, we thought that a non-selective (AMPA/glycine) profile might be more effective in inhibiting delayed neuronal death, the latter being known to occur after head trauma and stroke. Indeed, taking into account the way EAA-sensitive neurones operate, AMPA induced currents are expected to induce the depolarization which will remove the voltage-dependent magnesium block of the NMDA–glycine receptor, thus leading to excitotoxicity.

When the different tautomeric forms of the quinoxalinediones (Fig. 2) are considered, we speculated that the isosteric replacement of one hydroxyl function by an acidic sulfonylamino group could lead to a new class of antagonists endowed with more favorable physico-chemical properties in addition to exerting powerful pharmacological effects.

In this paper we describe the result of work based on these hypotheses, which led us to the design and synthesis of a new class of molecules, the 3-sulfonylamino-2-(1*H*)-quinolones. These compounds were found to be potent antagonists at both the AMPA/kainate site as well as at the NMDA-associated glycine site.

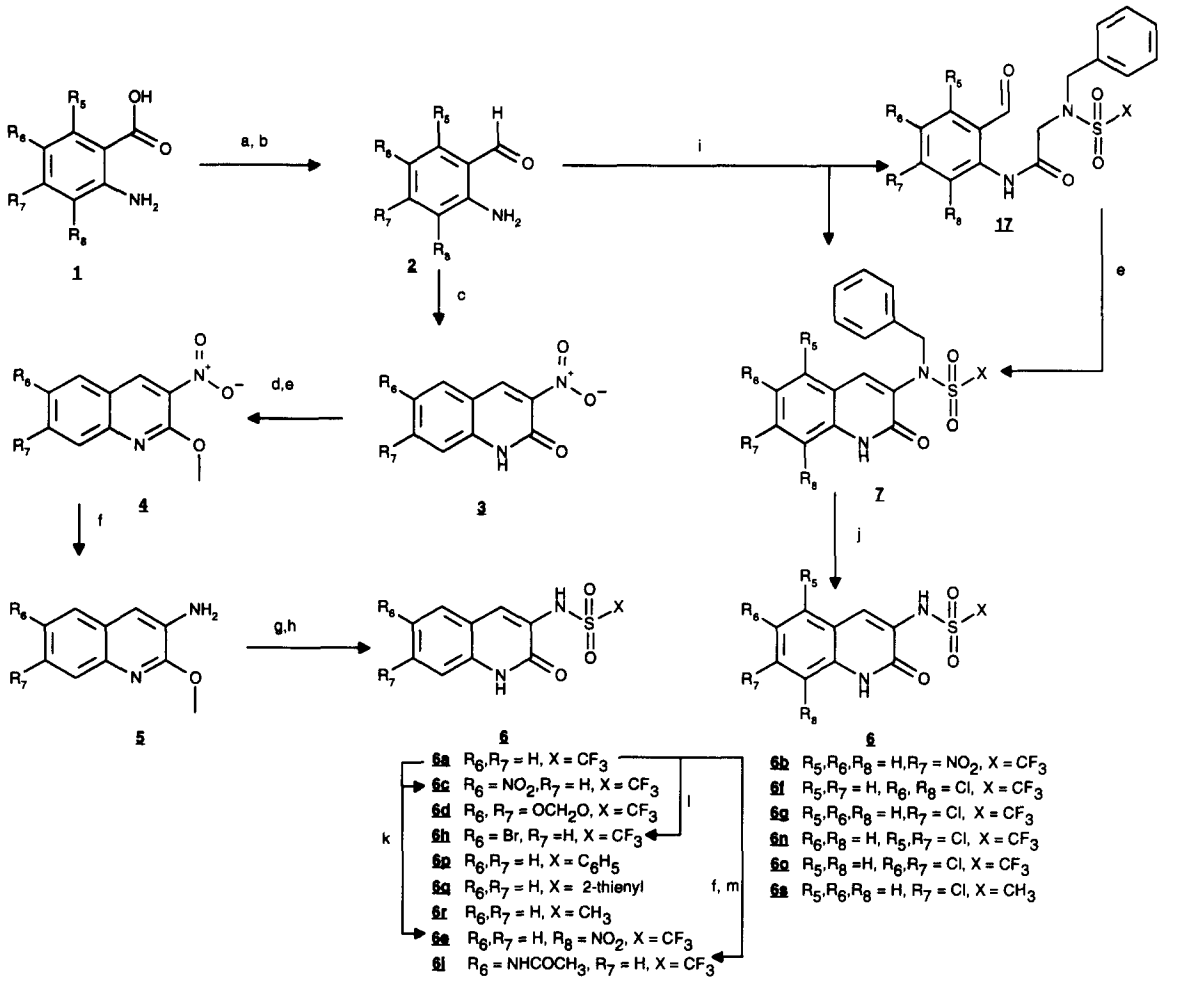
Synthesis

The compounds of interest were synthesized by two different routes (Fig. 3), both starting from the same anthranilic aldehyde intermediates **2** which are themselves easily prepared from the corresponding known acids **1**[15] through a reduction–oxidation step. Some of these anthranilic acids were synthesized by the isatine route.[16] The synthesis of the parent compound **6a** was first attempted through trifluoromethane-sulfonylation of 3-amino-2-(1*H*)-quinolone[17] but the reaction led to a mixture of compounds resulting from O and N' sulfonylation. We therefore embarked on an additional protection step by transforming the quinolone to the 2-methoxy quinoline **4**. After reduction of the nitro function with stannous chloride, the amine was sulfonylated with trifluoromethanesulfonic anhydride and the 2-methoxy quinoline was deprotected under acidic conditions.

Owing to the sensitivity of some aromatic substituents to the reductive conditions used in the first approach, an alternative synthesis was devised by a modification of the method of F. Bahr:[18] the aldehydes were condensed with 2-(*N*-benzyl-*N*-trifluoromethanesulfonylamino)-acetyl chloride **16** in the presence of triethylamine which gave the corresponding acylated anthranilic aldehyde, and the ring closure was then accomplished through the action of a strong base (sodium methoxide in methanol). In one case, starting with the aldehyde **2f**, the cyclization occurred spontaneously and the 2-(1*H*)-quinolone **7f** was directly obtained. Depending on the substitution, the debenzylation was carried out smoothly either by the action of aluminium chloride in dichloromethane,[19] or by hydrogenation in ethanol with Pd/C as catalyst.

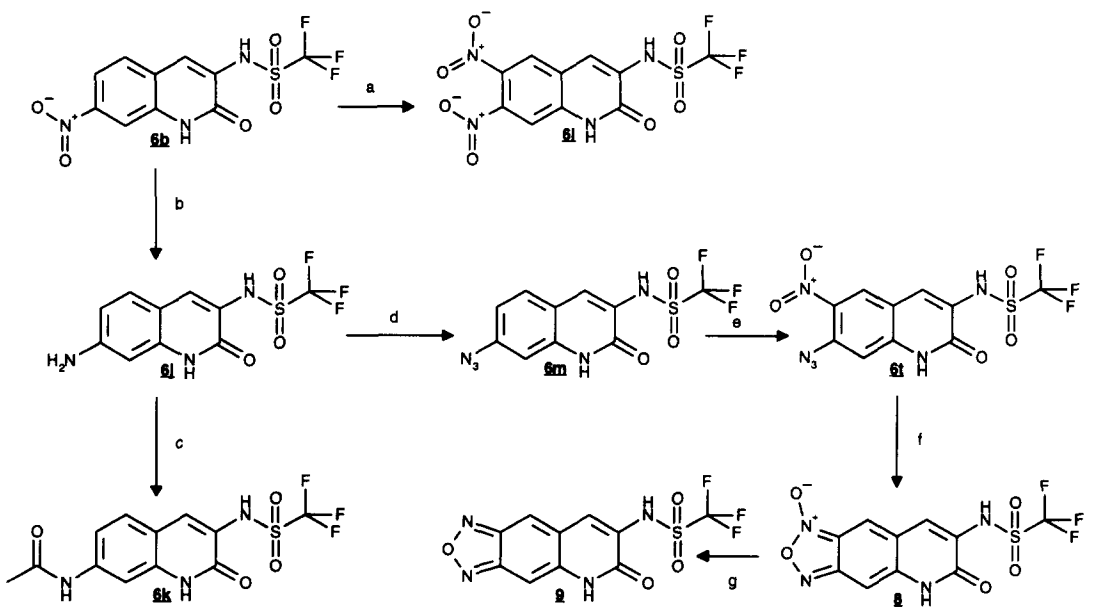
Some of the compounds studied were prepared through the derivatization of 3-trifluoromethanesulfonylamino-2-(1*H*)-quinolones. Indeed, after bromination of the parent compound **6a** with bromine in acetic acid, the 6-bromo derivative **6h** was isolated; after nitration of the same starting material in a mixture of sulfuric and nitric acid, the 6-nitro **6c** as well as the 8-nitro **6e** derivatives were obtained.

One particularly appealing substitution was the oxadiazole **9** which was elaborated through a five step sequence (Fig. 4) from the 7-nitro derivative **6b**. Reduction of the nitro group afforded the amino group which was diazotized by sodium nitrite in aqueous tetrafluoroboric acid in the presence of azide ions. The azide **6m** was carefully nitrated, at 0 °C, in position 6 by nitric acid and the nitro-azide was thermolyzed in refluxing toluene leading to the oxadiazole oxide **8** which was



Reagents and Conditions: (a) $LiAlH_4$, THF or BH_3·Me_2S, THF; (b) MnO_2, CH_2Cl_2 or THF; (c) Ethyl nitroacetate, o-Xyleneopropylamine; (d) $OPCl_3$; (e) MeONa, MeOH; (f) $SnCl_2$, EtOH; (g) $(XSO_2)_2O$, Et_3N, CH_2Cl_2; (h) H^+/H_2O; (k) 2-(N-benzyl-N-trifluoromethanesulfonyl-amino)-acetyl chloride **16**, Et_3N, THF; (j) $AlCl_3$, CH_2Cl_2 or Pd/C, H_2, EtOH; (k) HNO_3, H_2SO_4; (l) Br_2, AcOH; (m) Ac_2O, Et_3N, THF.

Figure 3.



Reagents and conditions: (a) HNO_3, H_2SO_4; (b) $SnCl_2$, EtOH; (c) Ac_2O, Et_3N, THF; (d) HBF_4, $NaNO_2$, NaN_3; (e) HNO_3; (f) Toluene, 100 °C; (g) $(C_6H_5)_3P$, acetone.

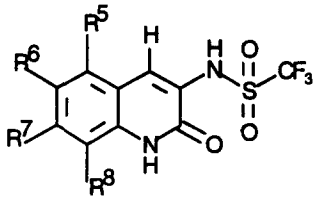
Figure 4.

deoxygenated by triphenylphosphine in acetone, at room temperature.

Results and Discussion

The results of the biological evaluation of compounds **6a–s**, **8** and **9** are presented in Tables 1 and 2. Our previous investigations on quinoxalinedione derivatives[12] had shown that, in *Xenopus* oocytes injected with rat cerebral cortex mRNA, the antagonism of AMPA and kainate responses are fairly parallel indicating that both agonists activate the same AMPA-type receptor channels. We therefore elected to challenge the oocytes by kainate and

Table 1. Influence of aromatic substitution on *in vitro* pharmacological data. In the *Xenopus* oocyte assays, IC_{50} values were derived from inhibition curves constructed with data from four to eight experiments at each drug concentration. In the binding assays, the IC_{50} values were determined from inhibition curve fitting to 5–6 points, each point representing the mean value of duplicates. In most cases, enough experiments ($N > 5$) were conducted to calculate the corresponding standard deviations which were in the ± 49% of the mean value



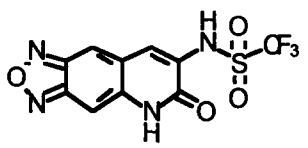
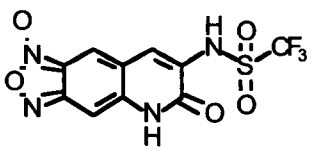
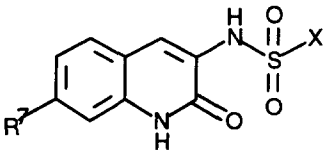
					Oocytes/électrophy. IC_{50} µM		Cortical Membranes Binding IC_{50} µM		
#	R^5	R^6	R^7	R^8	Kainate	NMDA/GLY	AMPA	GLY	MK801
NBQX					0,078	>60	0,06	>500	
6NQX					4,4	3,6	11		
DNQX					0,53	0,66	0,15	2,9	
6a	H	H	H	H	90	9,7	265	18,5	190
6b	H	H	NO_2	H	0,63	0,62	0,6	0,65	3,4
6c	H	NO_2	H	H	20	4,1	2,4		
6d	H	-O-CH_2-O-		H	22	24	5		
6e	H	H	H	NO_2	240	81			
6f	H	Cl	H	Cl	200	11	>500		
6g	H	H	Cl	H	4,3	0,81	4,2	1,45	2,4
6h	H	Br	H	H	40	4,9	100	50	
6i	H	CH_3CONH	H	H	50	32			
6j	H	H	NH_2	H	90	57	>250	169	>250
6k	H	H	CH_3CONH	H	300	49	>250	36	>250
6l	H	NO_2	NO_2	H	**0,16**	0,16	**0,09**	1,38	
6m	H	H	N_3	H	11	1,6			
6n	Cl	H	Cl	H	8	1,5	19	21	
6o	H	Cl	Cl	H	3,5	0,32	15	0,8	7,4
9					5	4,9	6,1	5,5	36
8					2,5	3,2			

Table 2. Influence of the sulfonylamino substitution on the *in vitro* pharmacological data. In the *Xenopus* oocyte assays, IC_{50} values were derived from inhibition curves constructed with data from four to eight experiments at each drug concentration. In the binding assays, the IC_{50} values were determined from inhibition curves fitting to 5–6 points, each representing the mean value of duplicates. In most cases, enough experiments ($N > 5$) were conducted to calculate the corresponding standard deviations which were in the ± 49% of the mean value



			Oocytes/électrophy. IC_{50} µM		Cortical Membranes Binding IC_{50} µM		
#	X	R^7	Kainate	NMDA/GLY	AMPA	GLY	MK801
6a	CF_3	H	90	9,7	265	18,5	
6p	Ph	H	400	>50			
6q	Thienyl	H	>300	>50			
6r	CH_3	H	900	>160			
6g	CF_3	Cl	4,3	0,81	4,2	1,45	2,4
6s	CH_3	Cl	60	>50	54	6	

to measure the displacement of [^{3}H]AMPA binding as an initial evaluation of the AMPA/kainate antagonist potency of our compounds.

It is clear from Table 2 that the strong electron-withdrawing trifluoromethane residue is the best substituent in the sulfonamide moiety in terms of affinity (binding assay), or antagonist potency (oocyte assay): **6a** > **6p** / **6q** > **6r** and **6g** > **6s**.

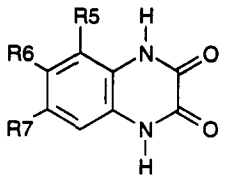
Because the symmetry which exists in the quinoxalinediones no longer prevails in the 3-sulfonylamino-2-(1*H*)-quinolone derivatives, four different mono-nitro substituted molecules could be envisaged. Three of them have been synthesized and evaluated. Among them, the 7-nitro isomer **6b** is the most powerful balanced AMPA/glycine antagonist, being 380-fold more potent than the 8-nitro isomer **6e** and 30-fold more potent in inhibiting kainate induced currents than the 6-nitro isomer **6c** which, surprisingly, is a glycine selective antagonist. Compound **6b** is 140-fold more potent than the unsubstituted parent compound **6a**; a similar dramatic effect of nitro substitution has already been reported in the NBQX series[20] where 2,3-dihydroxy-7-sulfamoyl-benzo[*f*]quinoxaline (BQX) is 180-fold less potent than its nitro analogue. A second nitro substituent led to the most potent compound of the series **6l**, this being 4-fold more potent than the mono-nitro parent compound **6b** (IC_{50}: 0.16 µM in both the kainate and glycine assays). This increase can be compared to the 8-fold potency increase induced by a second nitro substitution in the quinoxalinedione series, going from 6NQX to DNQX (Table 1). The difference between the two series may be explained by a favorable entropy factor brought about by the symmetry of DNQX.

Chloride substitutions are more difficult to analyze, as all the monosubstituted compounds are not available. However, chloride substitutions generally lead to more glycine-selective antagonists: **6f** 18-fold, **6g** 5-fold, **6n** 5-fold and **6o** 10-fold. As in kynurenic acid derivatives,[21] substitution at position 8 is least favored (**6f**), but in contrast the 5,7 disubstitution is not favored (**6n**) with regards to the glycine receptor, the more potent compound being the 6,7 dichloro derivative **6o**. The electron-donor aromatic substitutions systematically lead to inactive compounds (**6d**, **6i**, **6j** and **6k**).

These data indicate that an increase in the electronegativity of the aromatic substituents or of the sulfonamido substituents increases the affinity and efficacy of the compounds towards the AMPA/kainate and glycine receptors. This effect is particularly striking when the aromatic substituent is in position 7 where it could directly influence the acidity of the sulfonamido function through its mesomeric effect. We therefore thought that it might be possible to correlate the K_i generated by electrophysiology, with the measured pK_a values. Table 3 displays the estimates of pK_a for the series of quinoxalinedione reference compounds and some 3-sulfonylamino quinolone derivatives. It is worth noting that, after the titration procedure, several of the solutions were tested on *Xenopus* oocyte responses to kainate and no loss of antagonist activity was noted (data not shown). When the points were plotted (Figs 5 and 6), a straight line correlation was not obtained. However, for each type of structure (quinoxalinedione, ■; benzoquinoxalinedione, Δ; and 3-sulfonylamino quinolone, O) a good correlation ($R > 0.9$) could be found at least for the effect at the AMPA/kainate receptor (Fig. 5). In the case of the quinoxalinedione, the 5-substituted derivatives (5NQX, ONQX and MNQX) must be kept out of the correlation, reflecting a supposedly disfavorable steric impact of the substitution in this position. In the graph, the lines join pairs of compounds for which one compound lacks the nitro substitution (in position 6 or 7, 'pseudo-*para*'

position relative to the acidic group) that increases both acidity and AMPA/kainate receptor efficacy. It is apparent that nitro substitution in the 'pseudo-*para*' position (5NQX → MNQX; QX → 6NQX → DNQX; CNQX; BQX → NBQX) increases AMPA affinity roughly in proportion with the increase in the percentage of ionized species since the slope of these lines ($\Delta pK_i/\Delta pK_a$) is close to unity. However the analogous substitution in our series (**6a** → **6b**) increases affinity considerably without great effect on pK_a. Conversely, substantial increases in acidity may be accompanied by modest increases in potency when the nitro substitution is not in the 'pseudo-*para*' position (**6b** → **6l**) or is in a position sterically disfavorable (QX → 5NQX). This analysis indicates that the pK_a of the acidic function is an important, but not sufficient parameter for the high AMPA/kainate receptor efficacy. The appropriate positioning of electron-dense group is a second essential

Table 3. pK_a Values for quinoxalinediones and 3-sulfonylamino quinolone derivatives. Experimental data for all compounds are mean ± standard deviation of 3–4 determinations except where indicated



#	R5	R6	R7	pKa
QX	H	H	H	9.21±0.13
5NQX	NO_2	H	H	8.03±0.02
6NQX	H	NO_2	H	8.07±0.05
ONQX	NO_2	NO_2	H	5.18±0.02
MNQX	NO_2	H	NO_2	6.67±0.06
DNQX	H	NO_2	NO_2	7.09±0.03
CNQX	H	NO_2	CN	6.97±0.06
BQX	-CH=CH-CH=C(SO_2NH_2)-		H	8.33±0.34
NBQX	-CH=CH-CH=C(SO_2NH_2)-		NO_2	7.43±0.02
6a	H	H	H	5.25±0.10
6b	H	H	NO_2	5.23±0.23
6g	H	H	Cl	5.63±0.23
6l	H	NO_2	NO_2	3.65± (n=1)
6o	H	Cl	Cl	5.80± (n=1)

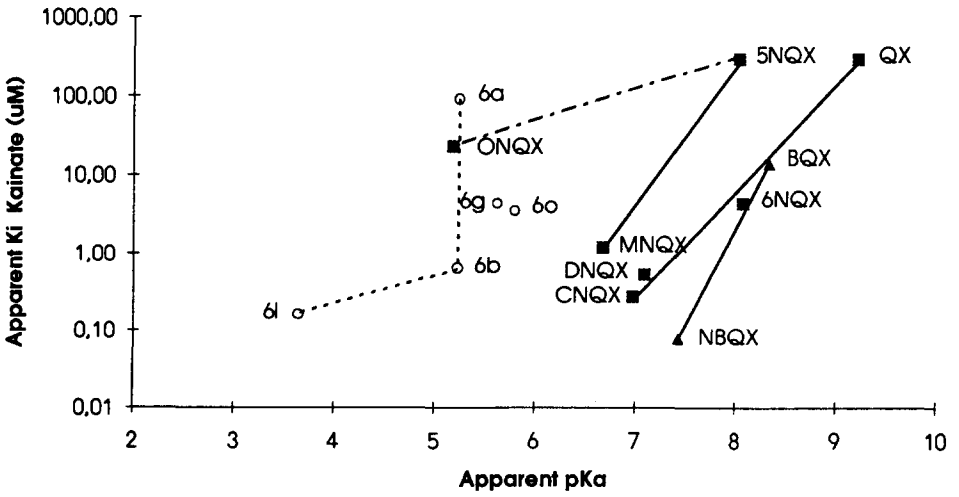


Figure 5. Comparison of apparent pK_a values of quinoxalinediones and 3-sulfonylamino quinolones versus the IC_{50} values of the same compounds for inhibition of kainate currents in mRNA-injected *Xenopus* oocytes. In the graph, the different chemical structures are represented as follows: quinoxalinedione, n; benzoquinoxalinedione, Δ; 3-sulfonylamino quinolone, °.

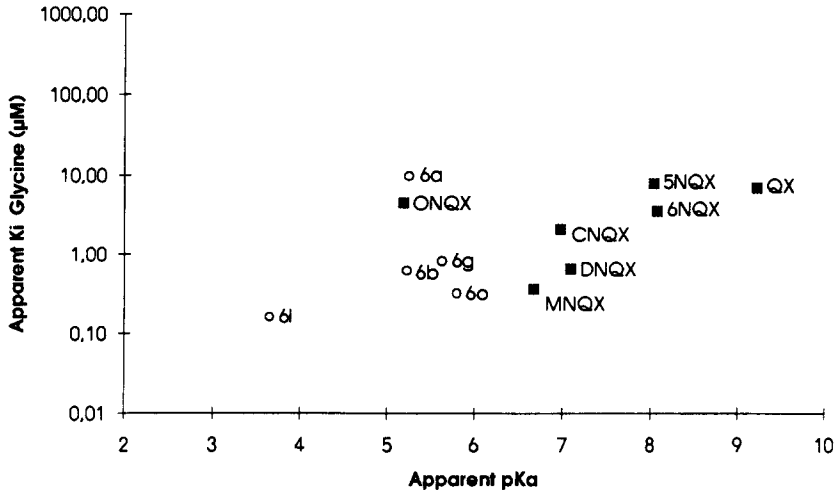


Figure 6. Comparison of apparent pK_a values of quinoxalinediones and 3-sulfonylamino quinolones versus the IC_{50} values of the same compounds for inhibition of glycine/NMDA currents in mRNA-injected *Xenopus* oocytes. In the graph, the different chemical structures are represented as follows: quinoxalinedione, ■; 3-sulfonylamino quinolone, O.

determinant. In contrast, the results related to the glycine receptor are less coherent and only a general trend could be deduced from Figure 6.

A disappointing result came from the oxadiazole **9** which is 30-fold less potent than the dinitro derivative **6l** from which it was designed as an isostere. It is worth noting that the N-oxide **8** is twice as potent as the oxadiazole. One would anticipate that the isomeric N-oxide would be a better mimic of the 7-nitro substitution and therefore an even more potent compound. These results allow us to speculate that for powerful AMPA/glycine antagonists, a high density of negative charge in the 6,7 position is more important than the electronegativity of the substituents in this area.

In conclusion, we have discovered a new class of balanced AMPA/glycine antagonists which demonstrate the validity of the isosteric replacement of an acidic hydroxyl function by a trifluoromethanesulfonylamide group. The structure–activity relationships which have been published earlier for the quinoxalinedione series[12] can be transferred easily to this new class of antagonists. We also found that the replacement of an *ortho* dinitro substitution by an oxadiazole led, in this series, to a profound loss of potency, in contrast to what has been published for dihydropyridine calcium antagonists[22] and among chroman Class III antiarrhythmic agents.[23]

The *in vivo* pharmacology of these compounds (data not shown) was very disappointing, due apparently to the poor brain bioavailability linked to their low solubility in physiological media.

Experimental Section

Biology

Xenopus *oocyte experiments.* Poly(A^+) messenger RNA isolated from rat cerebral cortex was injected in *Xenopus* oocytes[24] and the oocytes were incubated for 2–3 days at 18 °C to allow expression. They were then stored at 6–8 °C until use (typically 1–2 weeks); current responses to kainate, AMPA, and glycine/NMDA were thus maintained for as long as the oocytes remained viable. Kainate-induced currents were recorded in 'OR2' medium[25] of composition (in mM): NaCl 82.5; KCl 2.5; $CaCl_2$ 1; $MgCl_2$ 1; NaH_2PO_4 1; HEPES 5; pH 7.4. For the recording of NMDA/glycine currents, $MgCl_2$ was omitted from the medium and the concentration of $CaCl_2$ was raised to 2 mM. Experiments were performed using a two electrode voltage clamp with a third electrode placed in the bath as voltage reference. Glass microelectrodes (*ca* 1 MΩ) were filled with 3 M KCl. The holding potential was adjusted to –60 mV.

For the initial evaluation of the inhibitory potency of the compounds **6**, the agonists were applied at the following concentrations: kainate (100 µM) and glycine (3 µM)/NMDA (30 µM). The compounds **6** were bath applied for 30–45 s before and after the application of agonists, as well as during agonist application and responses were evaluated at the peak of the inward current.

Binding experiments. Membrane preparation. Rat cerebral cortices were homogenized in ice cold 0.32 M sucrose buffer (AMPA binding) or 50 mM Tris–acetate (glycine and MK 801 binding) and centrifuged at 1000 *g* for 10 min. The resulting supernatant was centrifuged at 37,000 *g* for 25 min, or at 40,000 *g* for 15 min, or at 25,000 *g* for 15 min, respectively. For AMPA binding the pellet was then washed in 30 mM Tris–HCl containing 2.5 mM $CaCl_2$, centrifuged as described above, lysed in distilled water and centrifuged again. The resulting pellet was then incubated with Triton TX-100 for 30 min at 25 °C, centrifuged and rinsed twice with Tris buffer then stored at –80 °C. For glycine binding, the pellet was washed three times with Tris–acetate buffer, suspended in 0.32 M sucrose buffer and frozen at –80 °C until further use. For MK 801 binding, the pellet was washed initially with 50 mM Tris–acetate buffer, then 5 mM Tris–HCl, lysed twice in distilled water and stored at –80 °C.

Binding assay.[26] The thawed membrane suspension (200 µL) was incubated in the presence of 25 µL of the ligand (*t* °C, time, concentration): [^{3}H]AMPA (4 °C, 30 min, 20 nM), [^{3}H]glycine (4°C, 60 min, 50 nM) and [^{3}H]MK 801 (25 °C, 2–6 h, 5 nM) and 25 µL of a known solution of compound **6**. Non-specific binding was defined in the presence of 100 µM quisqualic acid, 100 µM glycine or 30 µM MK 801, respectively. In saturation experiments, the specific binding was assayed over the range 0.1–300 nM in the absence (control) or presence of the drug to be tested. The membranes were collected by filtration using a Skatron cell harvester. Data were analyzed using Lundon software.

Estimation of pK_a value by titration. Acid dissociation constants were estimated using a conventional acid/base titration protocol with 1–2 mM test compound in an aqueous 120 mM NaCl solution containing 1% DMSO. Most of the compounds precipitated at acid pH and were maintained in suspension by a magnetic stirrer. Incremental addition of 0.25–1.0 µmol NaOH was performed, allowing sufficient time (1–10 min) for the pH to stabilize at each step. The pK_a was estimated to be equal to the pH observed at the point of minimum slope of the plot of pH versus acid/base equivalents occurring midway between two points of maximum slope.

Chemistry

All the compounds described were analyzed by infrared and NMR spectroscopy and demonstrated properties in accordance with the expected structures. In addition, elemental analyses for C, H, N, S, Cl were in the ± 0.4% range of the calculated values.

General procedure for the preparation of aminobenzaldehydes 2 (except when R = NO_2). The anthranilic acid was dissolved in anhydrous THF and cooled to 0 °C in an ice/water bath. $LiAlH_4$ (1.5 eq.) was added in small portions. When the addition was complete, the reaction was stirred at 0 °C for 15 min and then allowed to warm to room temperature over a period of approximately 1 h and then heated to reflux for 15 min. The reaction was cooled to 0 °C and the excess hydride was hydrolyzed by careful dropwise addition of an aqueous solution of THF:H_2O (2:1) until apparent reaction ceased. The precipitate was filtered off and washed several times with THF. To the filtrate, activated MnO_2 (2 eq.) was added and the reaction was stirred to reflux until TLC indicated consumption of starting material.

2-Amino-benzaldehyde 2a. The title compound was prepared in 33% yield starting from **1a** and purified by silica gel chromatography (hexane:ethyl acetate 75:25 and then ethyl acetate 100%); ^{1}H NMR ($CDCl_3$): 9.85 (*s*, 1H), 7.45 (*dd*, 1H), 7.3 (*td*, 1H), 6.75 (*td*, 1H), 6.65 (*dd*, 1H), 5.5–6.5 (*br s*, 2H).

2-Amino-4,5-methylenedioxy-benzaldehyde 2d. The title compound was prepared in 41% yield starting from **1d** and purified by silica gel chromatography (hexane:ethyl acetate 1:1 and then ethyl acetate 100%); mp (°C): 94–97; ^{1}H NMR ($CDCl_3$): 9.6 (*s*, 1H), 6.8 (*s*, 1H), 6.3 (*br s*, 2H), 6.15 (*s*, 1H), 5.9 (*s*, 1H).

2-Amino-3,5-dichloro-benzaldehyde 2f. The title compound was prepared in 58% yield starting from **1f** and purified by silica gel chromatography (hexane:ethyl acetate 1:1); mp (°C): 122; ^{1}H NMR ($CDCl_3$): 9.8 (*s*, 1H), 7.45 (*s*, 2H), 6.6 (*br s*, 2H). Anal. ($C_7H_5Cl_2NO$) C, H, N, Cl.

2-Amino-4-chloro-benzaldehyde 2g. The title compound was prepared in 71% yield starting from **1g** and purified by silica gel chromatography (hexane:ethyl acetate 1:1 and then ethyl acetate 100%); mp (°C): 77–80; ^{1}H NMR (DMSO-d_6): 9.8 (*s*, 1H), 7.60 (*d*, 1H), 7.0–7.8 (*br s*, 2H), 6.8 (*d*, 1H), 6.65 (*dd*, 1H). Anal. (C_7H_6ClNO) C, H, N, Cl.

2-Amino-4,6-dichloro-benzaldehyde 2n. The title compound was prepared in 84% yield starting from **1n** and purified by silica gel chromatography (toluene as eluant); mp (°C): 105; ^{1}H NMR ($CDCl_3$): 10.4 (*s*, 1H), 6.7 (*d*, 1H), 6.55 (*d*, 1H), 1.6 (*br s*, 2H). Anal. ($C_7H_5Cl_2NO$) C, H, Cl, N.

2-Amino-4,5-dichloro-benzaldehyde 2o. The title compound was prepared in 57% yield starting from **1o** and purified by recrystallization from toluene; mp (°C): 141–146; ^{1}H NMR ($CDCl_3$): 9.8 (*s*, 1H), 7.55 (*s*, 1H), 6.8 (*s*, 1H), 6.10 (*br s*, 2H). Anal. ($C_7H_5Cl_2NO$) C, H, Cl, N.

2-Amino-4-nitro-benzaldehyde 2b. To a solution of 5-nitro anthranilic acid (10 g, 55 mmol) in anhydrous THF (250 mL) was added dropwise a solution of borane–dimethylsulfide complex (11 mL, 110 mmol). The reaction was heated to reflux with stirring for 2 h and then cooled to 0 °C in an ice/water bath. Water (10 mL) was then added dropwise. When gaseous evolution had ceased, concentrated hydrochloric acid was added and the solution was heated to reflux for 30 min. The reaction mixture was poured on to crushed ice (500 g) and the aqueous phase was washed with methylene chloride (50 mL), alkalinized with concentrated aqueous sodium hydroxide solution and extracted several times with methylene chloride. The combined organic extracts were dried over magnesium sulfate, filtered and evaporated under vacuum to give 3-nitro-6-hydroxymethylaniline as a yellow solid (3.0 g, 32% yield); mp (°C): 130. To a solution of 3-nitro-6-hydroxymethylaniline (2.5 g, 15 mmol) in THF (50 mL), activated MnO_2 (9.5 g, 110 mmol) was added and the reaction was heated to reflux for 2.5 h. After cooling and filtration, the filtrate was evaporated under vacuum and the crude product was purified by chromatography on silica gel (cyclohexane:ethyl acetate 80:20) to give 2-amino-4-nitro-benzaldehyde as an orange solid (1.66 g, 66% yield); mp (°C): 126; ^{1}H NMR ($CDCl_3$): 10.0 (*s*, 1H), 7.7 (*d*, 1H), 7.5 (*s*, 1H), 7.5 (*d*, 1H), 6.5 (*br s*, 1H). Anal. ($C_7H_6N_2O$) C, H, N.

2-Methoxy-3-nitro-quinoline 4a. A solution of 3-nitro-2(1*H*)-quinolone[27] **3a** (1.50 g, 7.9 mmol) in phosphorous oxychloride was brought to reflux for 2 h. The excess

phosphorous oxychloride was evaporated under reduced pressure and the residual oil was dissolved in methylene chloride (50 mL). This organic phase was washed with water to neutral pH, dried and evaporated under vacuum. After dissolution of the residue in methanol (40 mL), a 1 N solution of sodium methoxide in methanol (10 mL) was added with stirring. The mixture was brought to reflux for 15 min. After cooling and evaporation of the methanol, the residue was taken up with methylene chloride (50 mL) and water (50 mL). The organic phase was separated, dried, the solvents were evaporated under vacuum and the crude product was purified by chromatography on silica gel (cyclohexane:ethyl acetate 90:10) to give 2-methoxy-3-nitro-quinoline as an orange solid (450 mg, 28% yield); mp (°C): 105; ^{1}H NMR ($CDCl_3$): 8.7 (*s*, 1H), 7.75–7.95 (*m*, 3H), 7.5 (*m*, 1H), 4.2 (*s*, 3H), 6.5 (*br s*, 1H).

2-Methoxy-3-amino-quinoline ***5a***. To a suspension of **4a** (1.59 g, 7.8 mmol) in ethanol (50 mL), stannous chloride dihydrate (8.80 g, 39 mmol) was added and the mixture was brought to reflux for 1 h. Chloroform (400 mL) and water (100 mL) were added to the solution which was alkalinized by adding aqueous sodium bicarbonate solution. The suspension was filtered, the organic phase was separated and the aqueous phase was extracted with chloroform. The combined organic extracts were dried, evaporated under vacuum and the crude product was purified by chromatography on silica gel (cyclohexane:ethyl acetate 90:10) to give 2-methoxy-3-amino-quinoline **5a** (0.50 g, 40% yield); mp (°C): 84; ^{1}H NMR (DMSO-d_6): 7.5–7.7 (*m*, 2H), 7.15–7.35 (*m*, 2H), 7.1 (*s*, 1H), 5.3–5.6 (*br s*, 2H), 4.0 (*s*, 3H).

2-Methoxy-3-(trifluoromethanesulfonylamino)-quinoline. To a solution of **5a** (550 mg, 3.2 mmol) in methylene chloride (50 mL) at 0 °C, triethylamine (330 mg, 3.3 mmol) was added, followed by the dropwise addition of trifluoromethanesulfonic anhydride (1.13 g, 4.0 mmol). The mixture was stirred for 3 min at 0 °C and 30 min at room temperature. After washing with 1 N HCl, the organic phase was extracted with 1N NaOH and then with water. The combined aqueous phases were acidified with 1 N HCl and extracted with methylene chloride. The organic phase was then dried over magnesium sulfate and evaporated to give 2-methoxy-3-(trifluoromethane-sulfonylamino)-quinoline as a white solid (950 mg, 97% yield); mp (°C): 84; ^{1}H NMR (DMSO-d_6): 8.25 (*s*, 1H), 7.95–7.70 (*m*, 3H), 7.50 (*m*, 1H), 4.05 (*s*, 3H). Anal. ($C_{11}H_9N_2O_3F_3S$) C, H, N, S.

*3-(Trifluoromethanesulfonylamino)-2(1*H*)-quinolone* ***6a***. A solution of 2-methoxy-3-(trifluoromethane-sulfonyl-amino)-quinoline (1.0 g, 3.2 mmol) in a mixture of methanol (20 mL) and conc. HCl (10 mL) was stirred at reflux for 2 h and left overnight at room temperature. The precipitate was filtered and recrystallized from toluene to give **6a** (900 mg, 96% yield); mp (°C): 230; ^{1}H NMR (DMSO-d_6): 12.2 (*s*, 1H), 8.0 (*s*, 1H), 7.8–7.3 (*m*, 4H). Anal. ($C_{10}H_7N_2O_3F_3S$) C, H, N, S.

Using the procedure exemplified for **6a**, the following compounds were obtained:

*6,7-Methylenedioxy-3-nitro-2(1*H*)-quinolone* ***3d***. 86% yield; ^{1}H NMR (DMSO-d_6): 12.5 (*br s*, 1H), 8.8 (*s*, 1H), 7.35 (*s*, 1H), 6.8 (*s*, 1H), 6.15 (*s*, 2H). Anal. ($C_{10}H_6N_2O_5$) C, H, N.

2-Methoxy-6,7-methylenedioxy-3-nitro-quinoline ***4d***. 79% yield; ^{1}H NMR ($CDCl_3$): 8.55 (*s*, 1H), 7.20 (*s*, 1H), 7.07 (*s*, 1H), 6.13 (*s*, 2H), 4.15 (*s*, 3H). Anal. ($C_{11}H_8N_2O_5$) C, H, N.

2-Methoxy-6,7-methylenedioxy-3-amino-quinoline ***5d***. 41% yield; mp (°C): 202; ^{1}H NMR (DMSO-d_6): 7.05–7.0 (*s* + *s*, 1H + 2 H), 6.05 (*s*, 2H), 5.15 (*s*, 2H), 3.95 (*s*, 3H).

2-Methoxy-6,7-methylenedioxy-3-trifluoromethanesulfonylamino-quinoline. 80% yield; mp (°C): 198; ^{1}H NMR (DMSO-d_6): 8.05 (*s*, 1H), 7.35 (*s*, 1H), 7.2 (*s*, 1H), 6.2 (*s*, 2H), 4.0 (*s*, 3H). Anal. ($C_{12}H_9F_3N_2O_5S$) C, H, N, S.

*6,7-Methylenedioxy-3-trifluoromethanesulfonylamino-2(1*H*)-quinolone* ***6d***. 75% yield; mp (°C): > 260; ^{1}H NMR (DMSO-d_6): 12.15 (*br s*, 1H), 7.9 (*s*, 1H), 7.3 (*s*, 1H), 6.85 (*s*, 1H), 6.1 (*s*, 2H). Anal. ($C_{11}H_7F_3N_2O_5S$) C, H, N, S.

*3-Benzenesulfonylamino-2(1*H*)-quinolone* ***6p***. *(a) 3-Benzenesulfonylamino-2-methoxy-quinolone*. To a solution of amine **5a** (1.0 g, 5.74 mmol) in chloroform (100 mL) and pyridine (0.46 mL, 5.74 mmol), benzene-sulfonyl chloride (0.14 mL, 1.53 mmol) was added dropwise. The reaction was heated to reflux overnight. After cooling the organic phase was washed with 1 N HCl (3 × 30 mL) and extracted with 1 N NaOH (2 × 20 mL). The basic aqueous phase was acidified with 1 N HCl and extracted several times with methylene chloride. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and evaporated under vacuum to yield 3-benzenesulfonylamino-2-methoxy-quinoline as a white solid (1.12 g, 62% yield). mp (°C): 198–203; ^{1}H NMR (DMSO-d_6): 8.05 (*s*, 1H), 7.85 (*m*, 3H), 7.4–7.7 (*m*, 5H), 7.35 (*m*, 1H), 3.8 (*s*, 3H). Anal. ($C_{16}H_{14}N_2O_3S$) C, H, N, S.

(b) *3-Benzenesulfonylamino-2(1*H*)-quinolone* ***6p***. A solution of 3-benzenesulfonylamino-2-methoxy-quinoline (975 mg, 3.10 mmol) in a mixture of methanol (20 mL) and conc. HCl (10 mL) was heated to reflux with stirring for 2 h. The precipitate was filtered to give **6p** (733 mg, 79% yield); mp (°C): 235; ^{1}H NMR (DMSO-d_6): 12.15 (*br s*, 1H), 9.7 (*br s*, 1H), 8.1 (*s*, 1H), 7.95 (*dd*, 2H), 7.8 (*s*, 1H), 7.7 (*dd*, 1H), 7.5–7.65 (*m*, 3H), 7.4 (*td*, 1H), 7.2 (*dd*, 1H) 7.15 (*td*, 1H). Anal. ($C_{15}H_{12}N_2O_3S$) C, H, N, S.

Using the procedure exemplified for **6p**, the following compounds **6q** and **6r** were obtained:

3-(2-Thiophenesulfonylamino)-2-methoxy-quinoline. From the reaction of **5a** and thiophenesulfonyl chloride. 30% yield; mp (°C): 242; ^{1}H NMR (DMSO-d_6): 10.3 (*br s*, 1H), 8.2 (*s*, 1H), 7.9 (*d*, 2H), 7.7 (*t*, 1H), 7.7–7.5 (*m*, 2H), 7.45 (*t*, 1H), 7.15 (*t*, 1H), 3.85 (*s*, 3H).

3-(2-Thiophenesulfonylamino)-2(1H)-quinolone **6q**. 84% yield; mp (°C): 240; ^{1}H NMR (DMSO-d_6): 12.2 (*br s*, 1H), 9.8 (*br s*, 1H), 7.9 (*m*, 2H), 7.85 (*s*, 1H), 7.75 (*m*, 2H), 7.45 (*td*, 1H), 7.3–7.05 (*m*, 3H). Anal. ($C_{10}H_{10}N_2O_3S$) C, H, N, S.

3-Methanesulfonylamino-2-methoxy-quinoline. From the reaction of **5a** and methanesulfonic anhydride. 44% yield; mp (°C): 124; ^{1}H NMR (DMSO-d_6): 9.45 (*br s*, 1H), 8.1 (*s*, 1H), 7.9 (*dd*, 1H), 7.75 (*dd*, 1H), 7.65 (*td*, 1H), 7.45 (*td*, 1H), 4.05 (*s*, 3H), 3.15 (*s*, 3H).

3-Methanesulfonylamino-2(1H)-quinolone **6r**. 97% yield; mp (°C): 252; ^{1}H NMR (DMSO-d_6): 12.25 (*br s*, 1H), 8.9 (*br s*, 1H), 7.8 (*s*, 1H), 7.7 (*dd*, 1H), 7.45 (*td*, 1H),7.3 (*dd*, 1H), 7.2 (*td*, 3H), 3.2 (*s*, 3H). Anal. ($C_{10}H_{10}N_2O_3S$) C, H, N, S.

2-(N-Benzyl-N-trifluoromethanesulfonylamino)acetyl chloride **16**. *N*-Benzyl ethyl glycinate (20 g, 103 mmol) was dissolved in anhydrous methylene chloride (100 mL), cooled to 0 °C in an ice/water bath and triethylamine (15.7 mL, 113 mmol) was added. To this solution, trifluoromethanesulfonic anhydride (17.4 mL, 103 mmol) was added dropwise and the reaction was stirred at 0 °C for 15 min. The organic phase was washed with water, dried over magnesium sulfate and evaporated to give an oil which was suspended in 1 N NaOH (150 mL). The mixture was stirred at 95–100 °C for 4 h. After cooling of the reaction medium to 0 °C, 1 N HCl (150 mL) was added dropwise with stirring. The reaction mixture was extracted with methylene chloride, the organic solution was dried over magnesium sulfate and evaporated to give a yellow solid which was dissolved in thionyl chloride (100 mL) and heated to reflux with stirring overnight. The excess thionyl chloride was evaporated under vacuum to give a white solid (28 g, 88% yield); ^{1}H NMR ($CDCl_3$): 7.45 (*m*, 3H), 7.3 (*m*, 3H), 4.0–5.0 (*m*, 4H). Anal. ($C_{10}H_9ClF_3NO_3S$) C, H, N,Cl, S.

3-[(N-Benzyl-N-trifluoromethanesulfonylamino)]-6,8-dichloro-2(1H)-quinolone **7f**. 2-Amino-3,5-dichlorobenzaldehyde **2f** (1.53 g, 8.05 mmol) was dissolved in anhydrous THF cooled to 0 °C in an ice/water bath and triethylamine (4.48 mL, 32.2 mmol) was added. To this mixture, a solution of 2-(*N*-benzyl-*N*-trifluoromethanesulfonylamino)acetyl chloride **16** (3.81 g, 12.08 mmol) in THF (20 mL) was added dropwise. When the addition was complete, a solid precipitated. The reaction mixture was stirred to reflux overnight and the precipitate salt was filtered off and washed several times with THF. The filtrate was evaporated and the residue was dissolved in methylene chloride. The organic phase was washed with 1 N NaOH and 1 N HCl, dried over magnesium sulfate, filtered and evaporated. The crude reaction mixture was purified by recrystallization in ethyl acetate to give **7f** as a white solid (0.453 mg, 13% yield). The starting amino-benzaldehyde was recovered by chromatography of the filtrate on silica gel column; mp (°C): 215; ^{1}H NMR (DMSO-d_6): 12.0 (*br s*, 1H), 8.0 (*d*, 1H), 7.85 (*m*, 2H), 7.2–7.4 (*m*, 5H), 5.05 (*s*, 2H). Anal. ($C_{17}H_{11}Cl_2F_3N_2O_3S$) C, H, Cl, N, S.

3-[(N-Benzyl-N-trifluoromethanesulfonylamino)]-7-chloro-2(1H)-quinolone **7g**. *(a)* *N-[2-(N-Benzyl-N-trifluoromethanesulfonylamino)acetyl]-3-chloro-6-formyl aniline* **17g**. 2-Amino-4-chloro-benzaldehyde **2g** (1.0 g, 6.43 mmol) was dissolved in anhydrous THF (50 mL) cooled to 0 °C in an ice/water bath and triethylamine (3.58 mL, 25.72 mmol) was added. To this solution, 2-(*N*-benzyl-*N*-trifluoromethanesulfonyl-amino) acetyl chloride (3.05 g, 9.64 mmol)) was added dropwise. When the addition was completed, a solid precipitated. The reaction mixture was stirred to reflux for 3 h and the precipitate salt was filtered off and washed several times with THF. The filtrate was evaporated and the residue was dissolved in methylene chloride. The organic phase was washed with 1 N NaOH and 1 N HCl, dried over magnesium sulfate, filtered and evaporated. The crude reaction mixture was purified by chromatography on silica gel column (methylene chloride) to give *N*-[2-(*N*-benzyl-*N*-trifluoromethanesulfonylamino)acetyl]-3-chloro-6-formyl aniline **17g** as a white solid (940 mg, 68% yield); mp (°C): 148; ^{1}H NMR (DMSO-d_6): 10.85 (*s*, 1H), 9.9 (*s*, 1H), 8.1 (*d*, 1H), 7.9 (*d*, 1H), 7.2–7.5 (*dd* + *m*, 6H), 4.7 (*m*, 2H) 4.3 (*m*, 2H). Anal. ($C_{17}H_{14}ClF_3N_2O_4S$) C, H, Cl, N, S.

(b) *3-[(N-Benzyl-N-trifluoromethanesulfonylamino)]-7-chloro-2(1H)-quinolone* **7g**. To a solution of *N*-[2-(*N*-benzyl-*N*-trifluoromethanesulfonylamino)acetyl]-3-chloro-6-formyl aniline **17g** (1.43 g, 3.4 mmol) in THF (30 mL), a methanolic solution of sodium methoxide (5.5 M, 0.93 mL, 5.1 mmol) was added and the reaction was stirred at 60 °C for 10 min. The reaction mixture was neutralized with 1 N HCl, water (50 mL) was added and the solution was extracted with ethyl acetate. The organic solution was washed with brine and dried over magnesium sulfate. The crude product was purified by chromatography on silica gel (methylene chloride 100% and then a mixture with ethyl ether 10% as eluant): 640 mg, 45% yield; mp (°C): 250; ^{1}H NMR (DMSO-d_6): 12.4 (*br s*, 1H), 7.95 (*d*, 1H), 7.7 (*d*, 1H), 7.1–7.4 (*d* + *dd* + *m*, 1H + 1H + 7H), 5.0 (*s*, 2H). Anal. ($C_{17}H_{12}Cl\ F_3N_2O_3S$) C, H, Cl, N, S.

Using the procedure exemplified for **7g**, the following compounds were obtained:

N-[2-(N-Benzyl-N-trifluoromethanesulfonylamino)acetyl]-3-nitro-6-formylaniline **17b**. 9% yield; ^{1}H NMR (DMSO-d_6): 10.9 (*br s*, 1H), 10.0 (*s*, 1H), 8.7 (*d*, 1H), 8.15 (*dd*, 1H), 8.05 (*d*, 1H), 7.2–7.5 (*m*, 5H), 4.7 (*m*, 2H), 4.4 (*m*, 2H).

3-[(N-Benzyl-N-trifluoromethanesulfonylamino)]-7-nitro-2(1H)-quinolone **7b**. Purified by silica gel column chromatography eluted with a mixture of hexane:ethyl acetate 9:1. 62% yield. ^{1}H NMR (DMSO-d_6): 12.7 (*br s*, 1H), 8.2 (*s*, 1H), 8.15 (*d*, 2H), 8.0 (*m*, 2H), 7.3 (*m*, 5H), 5.05 (*br s*, 2H).

N-[2-(N-Benzyl-N-trifluoromethanesulfonylamino)acetyl]-3,5-dichloro-6-formylaniline **17n**. 26% yield; mp (°C): 120; ^{1}H NMR (DMSO-d_6): 11.2 (*s*, 1H), 10.25 (*s*, 1H), 8.2

(*d*, 1H), 7.6 (*d*, 1H), 7.2–7.5 (*m*, 5H), 4.5–4.9 (*m*, 2H), 4.2–4.4 (*m*, 2H).

*3-[(*N*-Benzyl-*N*-trifluoromethanesulfonylamino)]-5,7-dichloro-2(1*H*)-quinolone* **7n**. Recrystallized from diisopropyl ether in 37% yield; mp (°C): 195–226; ^{1}H NMR (DMSO-d_6): 12.5–13.0 (*br s*, 1H), 7.75 (*s*, 1H), 7.55 (*d*, 1H), 7.2–7.4 (*m* + *d*, 6H), 5.05 (*s*, 2H).

*N-[2-(*N*-Benzyl-*N*-trifluoromethanesulfonylamino)acetyl]-3,4-dichloro-6-formylaniline* **17o**. 47% yield; mp (°C): 175–183; ^{1}H NMR (DMSO-d_6): 10.7–10.9 (*br s*, 1H), 9.9 (*s*, 1H), 8.15 (*s*, 1H), 8.05 (*s*, 1H), 7.6–7.15 (*m*, 5H), 4.9–4.5 (*m*, 2H), 4.35 (*m*, 2H).

*3-[(*N*-Benzyl-*N*-trifluoromethanesulfonylamino)]-6,7-dichloro-2(1*H*)-quinolone* **7o**. 52% yield; mp (°C): 235–245; ^{1}H NMR (DMSO-d_6): 12.5 (*br s*, 1H), 8.05 (*s*, 1H), 7.95 (*s*, 1H), 7.5 (*s*, 1H), 7.3 (*m*, 5H), 5.0 (*s*, 2H). Anal. ($C_{17}H_{11}Cl_2F_3N_2O_3S$) C, H, Cl, N, S.

General procedure for the N*-debenzylation (except when R = NO$_2$).* The *N*-benzyl derivative was dissolved in ethyl alcohol and the solution was hydrogenated with Pd/C 10% as catalyst for 6–24 h at atmospheric pressure. The catalyst was filtered and the solvent evaporated. The residue was diluted in methylene chloride and extracted with 1 N NaOH. The aqueous phase was acidified with 1 N HCl and the precipitate filtered.

3-(Trifluoromethylsulfonylamino)-6,8-dichloro-2(1H)-quinolone **6f**. Purified by crystallization from ethyl alcohol: 77% yield; mp (°C): 215; ^{1}H NMR (DMSO-d_6): 11.5–12.2 (*br s*, 1H), 7.95 (*s*, 1H), 7.90 (*d*, 1H), 7.80 (*d*, 1H). Anal. ($C_{10}H_5Cl_2F_3N_2O_3S$) C, H, Cl, N, S.

*7-Chloro-3-(trifluoromethanesulfonylamino)-2(1*H*)-quinolone* **6g**. Purified by crystallization from ethyl alcohol: 69% yield; mp (°C): > 260; ^{1}H NMR (DMSO-d_6): 12.3 (*br s*, 1H), 8.0 (*s*, 1H), 7.8 (*d*, 1H), 7.35 (*s*, 1H), 7.3 (*d*, 1H). Anal. ($C_{10}H_6ClF_3N_2O_3S$) C, H, Cl, N, S.

*5,7-Dichloro-3-(trifluoromethanesulfonylamino)-2(1*H*)-quinolone* **6n**. Purified by crystallization from acetonitrile: 75% yield; mp (°C): 254–256; ^{1}H NMR (DMSO-d_6): 12.4–12.8 (*br s*, 1H), 8.0 (*s*, 1H), 7.55 (*d*, 1H), 7.35 (*d*, 1H). Anal. ($C_{10}H_5Cl_2F_3N_2O_3S$) C, H, Cl, N, S.

*6,7-Dichloro-3-(trifluoromethanesulfonylamino)-2(1*H*)-quinolone* **6o**. Purified by crystallization from acetonitrile: 92% yield; mp (°C): 289–291; ^{1}H NMR (DMSO-d_6): 12.3–12.6 (*br s*, 1H), 8.1 (*s*, 1H), 8.0 (*d*, 1H), 7.5 (*s*, 1H). Anal. ($C_{10}H_5Cl_2F_3N_2O_3S$) C, H, Cl, N, S.

*7-Nitro-3-(trifluoromethanesulfonylamino)-2(1*H*)-quinolone* **6b**. Aluminum chloride (800 mg, 6 mmol) was added in small portions to a solution of **7b** (613 mg, 1.2 mmol) in dichloromethane (20 mL) at room temperature. The mixture was stirred for 2 h and then poured on to ice (50 mL) with the addition of 1 N hydrochloric acid (20 mL). After extraction of the aqueous phase with ethyl acetate, the organic phase was dried over magnesium sulfate and evaporated. The expected product was obtained after purification by chromatography on silica gel, eluted with a dichloromethane:ethanol:acetic acid (95:4.5:0.5) mixture. It was crystallized in a toluene:ethyl acetate (9:1) mixture to give a pale yellow solid (280 mg, 69% yield); mp (°C): 240; ^{1}H NMR (DMSO-d_6): 12.30 (s, 1H), 7.88–8.10 (*m*, 4H). Anal. ($C_{10}H_6F_3N_3O_5S$) C, H, N, S.

*6-Nitro-3-(trifluoromethanesulfonylamino)-2(1*H*)-quinolone* **6c** *and 8-nitro-3-(trifluoromethanesulfonylamino)-2(1*H*)-quinolone* **6e**. These two compounds were obtained by nitration of **6a**. A solution containing 86% nitric acid (2 mL) and concentrated sulfuric acid (1 mL) was prepared at 0 °C. This solution (0.33 mL) was added dropwise at 0 °C to a solution containing 1 g (3.4 mmol) of compound **6a** in concentrated sulfuric acid (2 mL) at 0 °C. The mixture was then stirred for 10 min at 0 °C and thereafter for 1.5 h at room temperature. After cooling of the reaction mixture to 0 °C, water (8 mL) was added dropwise with stirring. The yellow precipitate formed was filtered off, rinsed with water and dried. The two isomers were separated by column chromatography on silica gel, eluted with a dichloromethane:ethanol:acetic acid (90:9:1) mixture. The 8-nitro isomer was eluted first, and was recrystallized from an ethyl acetate:hexane mixture to give a yellow solid (80 mg, 7% yield); mp (°C): 205; ^{1}H NMR (DMSO-d_6): 11.4 (*br s*, 1H), 8.4 (*d*, 1H), 8.25 (*d*, 1H), 8.15 (*s*, 1H), 7.45 (*t*, 1H), 6.7 (*br s*, 1H). Anal. ($C_{10}H_6F_3N_3O_5S$) C, H, N, S. The 6-nitro isomer was obtained by further elution of the column. It was recrystallized from isopropanol to give a yellow solid (328 mg, 29% yield); mp (°C): > 260; ^{1}H NMR (DMSO-d_6): 12.8 (*br s*, 1H), 8.85 (*s*, 1H), 8.35 (*d*, 1H), 8.2 (*s*, 1H), 7.45 (*d*, 1H). Anal. ($C_{10}H_6F_3N_3O_5S$) C, H, N, S.

*6-Bromo-3-(trifluoromethanesulfonylamino)-2(1*H*)-quinolone* **6h**. To a suspension of **6a** (1 g, 3.4 mmol) in glacial acetic acid (4 mL), a solution of bromine (0.195 mL, 3.76 mmol) in glacial acetic acid (2 mL) was added dropwise. After stirring overnight at room temperature, water (10 mL) was added and the precipitate was filtered off to give a mixture of starting material and **6h**. This crude mixture was separated by chromatography on silica gel, using a dichloromethane:ethanol:acetic acid (90:9.5:0.5) mixture as eluant to give **6h** as a white solid (220 mg, 17% yield) which was recrystallized from ethanol: mp (°C): > 260; ^{1}H NMR (DMSO-d_6): 12.4 (*br s*, 1H), 8.05 (*s*, 1H), 8.00 (*s*, 1H), 7.70 (*d*, 1H), 7.30 (*d*, 1H). Anal. ($C_{10}H_6F_3N_2O_3SBr$) C, H, N, Br, S.

*6,7-Dinitro-3-(trifluoromethanesulfonylamino)-2(1*H*)-quinolone* **6l**. A solution of 86% nitric acid (1 mL) and concentrated sulfuric acid (2 mL) was prepared at 0 °C. This solution (0.275 mL) was added dropwise at 0 °C to a solution containing 1 g (2.96 mmol) of compound **6b** in concentrated sulfuric acid (2 mL) at 0 °C. The mixture was then stirred for 10 min at 0 °C and then allowed to warm to room temperature over a period of 1 h. After cooling of the reaction medium to 0 °C, water (5 mL) was added dropwise with stirring. The aqueous phase was

extracted several times with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered and evaporated under vacuum. The residue was chromatographed on silica gel (dichloromethane:ethanol:acetic acid 90:9.5:0.5) to yield **6l** as a yellow solid (287 mg, 25% yield): mp (°C): 236; ^{1}H NMR (DMSO-d_6): 8.60 (*s*, 1H), 7.90 (*s*, 1H), 7.80 (*s*, 1H). Anal. ($C_{10}H_5F_3N_4O_7S$) C, H, N, S.

7-Amino-3-(trifluoromethanesulfonylamino)-2(1H)-quinolone **6j**. To a suspension of **6b** (500 mg, 1.48 mmol) in ethanol (150 mL) was added stannous chloride dihydrate (1.35 g, 6.0 mmol) and the reaction mixture was heated to reflux with stirring for 1 h. The solvent was evaporated under vacuum and the residue was diluted with ethyl acetate (20 mL) and extracted with 3 N HCl (3 × 30 mL). The aqueous phase was neutralized with 3 N NaOH to pH 5–6 and extracted several times with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered and evaporated under vacuum. The residue was recrystallized from ethyl acetate/hexane to yield **6j** as a pale yellow solid (364 mg, 80% yield): mp (°C): 260; ^{1}H NMR (DMSO-d_6): 11.5–12.0 (*br s*, 1H), 5.0–9.0 (2H), 7.65 (*s*, 1H), 7.35 (*d*, 1H), 6.45 (*dd*, 1H), 6.35 (*d*, 1H). Anal. ($C_{10}H_8F_3N_3O_3S$) C, H, N, S.

7-Acetamido-3-(trifluoromethanesulfonylamino)-2(1H)-quinolone **6k**. To a solution of **6j** (450 mg, 1.48 mmol) in THF (100 mL) was added triethylamine (0.22 mL, 1.62 mmol) and acetic anhydride (0.14 mL, 1.53 mmol) and the reaction was heated to reflux overnight. The solvent was evaporated under vacuum. The residue was diluted with ethyl acetate (20 mL), washed with 1 N HCl (3 × 30 mL) and extracted with 1 N NaOH. The aqueous phase was neutralized with 1 N HCl and extracted several times with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered and evaporated under vacuum. The residue was crystallized from ethanol to yield **6k** as a white solid (180 mg, 35% yield): mp (°C): > 300; ^{1}H NMR (DMSO-d_6): 12.2 (*br s*, 1H), 10.3 (*br s*, 1H), 8.0–8.5 (*br s*, 1H), 7.95 (*d*, 1H), 7.9 (*s*, 1H), 7.7 (*d*, 1H), 7.3 (*dd*, 1H), 2.1 (*s*, 3H). Anal. ($C_{12}H_{10}F_3N_3O_4S$) C, H, N, S.

6-Acetamido-3-(trifluoromethanesulfonylamino)-2(1H)-quinolone **6i**. Prepared by reduction followed by acetylation of **6c** following the procedure exemplified for **6k** through **6j**. The compound was purified by silica gel chromatography eluted with a dichloromethane:ethanol:acetic acid (90:9:1) mixture. 22% overall yield; mp (°C): > 260; ^{1}H NMR (DMSO-d_6): 12.2 (*br s*, 1H), 10.1 (*br s*, 1H), 8.0 (*d*, 1H), 7.95 (*s*, 1H), 7.6 (*dd*, 1H), 7.3 (*d*, 1H), 2.05 (*s*, 3H). Anal. ($C_{12}H_{10}F_3N_3O_4S$) C, H, N, S.

7-Azido-3-(trifluoromethanesulfonylamino)-2(1H)-quinolone **6m**. To a suspension of **6j** (400 mg, 1.3 mmol) in 20% aqueous solution of HBF_4 (16 mL) at 0 °C was added dropwise sodium nitrite (135 mg, 1.95 mmol) in water (3 mL) and the reaction mixture was stirred at 0 °C for 30 min. To the yellow reaction mixture, sodium azide (127 mg, 1.95 mmol) in water (3 mL) was added dropwise at 0 °C and the reaction mixture was stirred at 0 °C for 15 min and then allowed to warm to room temperature over a period of 3 h. Water (20 mL) was added and the reaction mixture was extracted with ethyl acetate (2 × 30 mL), the organic phase was washed with 3 N HCl (3 × 30 mL), dried over magnesium sulfate, filtered and concentrated to 10 mL under vacuum to give a precipitate which was filtered off and recrystallized from ethyl acetate to yield **6m** (310 mg, 72% yield): mp (°C): 235; ^{1}H NMR (DMSO-d_6): 12.0–12.4 (*br s*, 1H), 8.0 (*s*, 1H), 7.8 (*d*, 1H), 7.0 (*dd*, 1H), 7.0 (*s*, 1H). Anal. ($C_{10}H_6F_3N_5O_3S$) C, H, N, S.

7-Azido-6-nitro-3-(trifluoromethanesulfonylamino)-2(1H)-quinolone **6t**. To a solution of 86% HNO_3 (3.5 mL) at 0 °C was added in small portions **6m** (460 mg, 1.38 mmol) in water (3 mL). The solution was stirred at 0°C for 10 min and poured onto crushed ice. The yellow precipitate was filtered off, washed with water, dried under vacuum and recrystallized from ethyl acetate/hexane (272 mg, 52% yield): ^{1}H NMR (DMSO-d_6): 12.3–12.6 (*br s*, 1H), 8.7 (*s*, 1H), 8.15 (*s*, 1H), 7.3 (*s*, 1H).

6-Hydroxy-7-(trifluoromethanesulfonylamino)-(1,2,5-oxadiazolo)-[3,4-g]-quinolin-1-oxide **8**. A suspension of **6t** (272 mg, 0.72 mmol) in toluene (50 mL) was stirred at 100 °C for 4 h. The solvent was evaporated under vacuum and the residue was taken up in diethyl ether to yield a precipitate which was filtered off and recrystallized from diethyl ether: (160 mg, 64% yield): mp (°C): 285; ^{1}H NMR (DMSO-d_6): 12.1 (*br s*, 1H), 8.1 (*s*, 1H), 7.8 (*s*, 1H), 7.1 (*s*, 1H); MS (EI) m/z 350 (MH^+).

6-Hydroxy-7-(trifluoromethylsulfonylamino)-(1,2,5-oxadiazolo)-[3,4-g]-quinoline sodium salt **9**. Triphenylphosphine (177 mg, 0.67 mmol) was added to a solution of **8** (236 mg, 0.67 mmol) in acetone (50 mL). The mixture was stirred for 15 min at room temperature and evaporated to dryness. The residue was taken up in diethyl ether (20 mL) and the mixture was extracted with 1 N NaOH (2 × 10 mL). The aqueous phase was acidified with 1 N HCl and extracted with ethyl acetate. After drying ($MgSO_4$), the product **9** was obtained after chromatography on silica gel (ethyl acetate:methanol, 95:5) (110 mg, 49% yield): mp (°C): 236; ^{1}H NMR (DMSO-d_6): 11.6 (*m*, 1H), 7.95 (*s*, 1H), 7.3 (*s*, 1H), 7.25 (*s*, 1H); MS (CI) m/z 356 (MH^+); Anal. ($C_{10}H_4F_3N_4NaO_4S$) C, H, N, S.

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