Fluorinated Quinazolones III: Synthesis and CNS Depressant Activity of Fluorinated Quinazolone Derivatives

KRISHNA C. JOSHI *x, VIRENDRA K. SINGH *, DAULAT S. MEHTA *, RAMESH C. SHARMA ‡, and LALIT GUPTA ‡

Abstract □ The synthesis of 2-allylthio-3-(4′-fluorophenyl)-5,6,7,8-tetrafluoro-4-quinazolone, 2-*n*-propylthio-3-(4′-fluorophenyl)-5,6,7,8-tetrafluoro-4-quinazolone, 3-(4′-bromophenyl)-5,6,7,8-tetrafluoro-2,4-quinazolinedithione, and seven fluorinated 2-alkyl/phenyl-3-aryl-4(3*H*)-quinazolones is described. The synthesized compounds were screened for CNS depressant activity using pentobarbital sleeping time, pentylenetetrazol convulsions, and condition avoidance test as the parameters. Most of the screened compounds exhibited significant depressant activity.

Keyphrases □ Quinazolone derivatives, fluorinated—synthesis and CNS depressant activity □ CNS depressant activity—synthesis and evaluation of fluorinated quinazolone derivatives

Since the introduction of methaqualone [2-methyl-3-(*o*-tolyl)-4(3*H*)-quinazolone] into clinical therapy as a nonbarbiturate hypnotic drug (1, 2), various 4(3*H*)-quinazolones and thioquinazolones have been investigated for pharmacological activity, including analgesic (3, 4), antispasmodic (5, 6), antihistaminic (7), hypotensive (8), muscle relaxant (9), sedative (10–13), anesthetic (10–13), and tranquilizing (10–13) activities.

Recently, the synthesis and pharmacological evaluation of a number of fluorinated 2-alkyl-3-aryl-4(3*H*)-quinazolones, thioquinazolones (14, 15), 2-mercapto-3-alkyl/aryl- and 2-alkylthio-3-aryl-4(3*H*)-quinazolones, and 3-aryl-2,4-quinazolinedithione were reported. Some compounds exhibited pronounced CNS activity. This finding prompted the investigation of the polyfluorinated analogs of the more active fluorinated quinazolone derivatives. This paper reports the preparation and CNS depressant activity of such compounds.

EXPERIMENTAL[1]

Compounds I–III (Table I) were prepared by the condensation of *N*-acyl derivatives of tetrafluoroanthranilic acid with an appropriate aromatic amine in the presence of phosphorus trichloride. Compounds IV–VII were prepared similarly from *N*-acyl/aroyl derivatives of 3- or 4-fluoroanthranilic acids. Compounds VIII and IX were prepared in good yield by refluxing tetrafluoroanthranilic acid and the corresponding phenylisothiocyanate in ethanol. On treatment with allyl chloride and *n*-propyl chloride, VIII was converted into the corresponding allylthio (X) and *n*-propylthio (XI) derivatives, respectively.

The treatment of IX with phosphorus pentasulfide in dry xylene gave 3-(4′-bromophenyl)-5,6,7,8-tetrafluoro-2,4-quinazolinedithione (XII) in quantitative yield.

Synthesis—*2-Methyl-3-(4′-bromophenyl)-5,6,7,8-tetrafluoro-4(3H)-quinazolone (I, Table I)*—To a solution of *N*-acetyl-2,3,4,5-tetrafluoroanthranilic acid (0.01 mole) and *p*-bromoaniline (0.01 mole) in dry toluene (20 ml) was added a solution of phosphorus trichloride (0.46 g, 0.0033 mole) in 5 ml of dry toluene, dropwise with constant stirring over 20 min. The resulting solution was further refluxed for 4 hr with constant stirring. After cooling, the reaction mixture was treated with 20 ml of 10% aqueous sodium carbonate solution and steam distilled to remove the toluene. The precipitated solid mass was removed by filtration, washed well with water, and recrystallized from ethanol using activated charcoal.

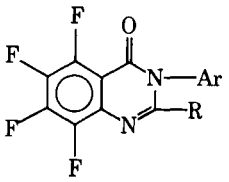
Other quinazolones (II–VII, Table I) were synthesized in a similar manner.

2-Mercapto-3-(4′-fluorophenyl)-5,6,7,8-tetrafluoro-4-quinazolone (VIII)—To a solution of tetrafluoroanthranilic acid (2.09 g, 0.01 mole) in 20 ml of ethanol, 4-fluorophenylisothiocyanate (1.53 g, 0.01 mole) was added. The resulting solution was heated under reflux for 2 hr when a crystalline solid mass was obtained. The solid mass was separated by filtration, washed with cold water, and recrystallized from acetic acid.

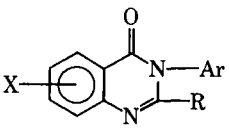
2-Mercapto-3-(4′-bromophenyl)-5,6,7,8-tetrafluoro-4-quinazolone (IX) was prepared in a similar manner.

2-Allylthio-3-(4′-fluorophenyl)-5,6,7,8-tetrafluoro-4-quinazolone (X)—To a solution of sodium hydroxide (0.63 g, 0.019 mole) in 15 ml of 50% ethanol, 2-mercapto-3-(4′-fluorophenyl)-5,6,7,8-tetrafluoro-4-quinazolone (1.77 g, 0.005 mole) was added and the mixture was stirred until a clear solution was obtained. Allyl chloride (0.456 g, 0.006 mole) was then added, and the solution was further stirred for 2 hr at room temperature. After cooling the resulting solution to 0°, the product was removed by filtration, washed with cold water, and recrystallized from aqueous ethanol to give a pure compound.

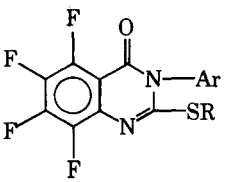
2-*n*-Propylthio-3-(4′-fluorophenyl)-5,6,7,8-tetrafluoro-4-quinazolone (XI) was prepared in a similar manner using *n*-propyl chloride.



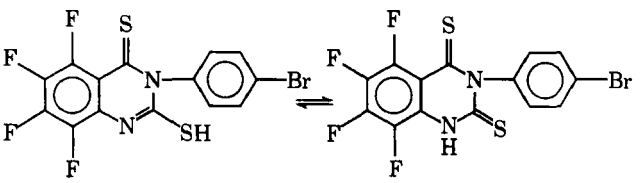
I: R = CH_3, Ar = 4-BrC_6H_4
II: R = CH_3, Ar = 2-$CH_3C_6H_4$
III: R = C_2H_5, Ar = C_6H_5



IV: X = 7-F, R = C_6H_5, Ar = C_6H_5
V: X = 7-F, R = C_6H_5, Ar = 2-$CH_3C_6H_4$
VI: X = 6-F, R = CH_3, Ar = 2-$CH_3C_6H_4$
VII: X = 7-F, R = CH_3, Ar = 2-$CH_3C_6H_4$



VIII: R = H, Ar = 4-FC_6H_4
IX: R = H, Ar = 4-BrC_6H_4
X: R = CH_2=CH—CH_2, Ar = 4-FC_6H_4
XI: R = CH_3—CH_2—CH_2, Ar = 4-FC_6H_4



XII

[1] All melting points are uncorrected. IR spectra were determined (Nujol mull) on a Perkin-Elmer model 337 grating IR spectrophotometer.

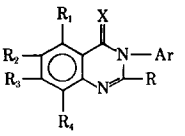


Table I—Fluorinated 2-Alkyl/phenyl-3-aryl-4(3*H*)-quinazolones and 2-Thio/alkylthio-3-aryl-4(3*H*)-quinazolones and Thioquinazolones

Compound	Ar	R	R_1	R_2	R_3	R_4	X	Molecular Formula	Analysis, %	Calc.	Found	Melting Point	Yield, %
I	4-BrC_6H_4	CH_3	F	F	F	F	O	$C_{15}H_7BrF_4N_2O$	N	7.23	7.17	165°	63
II	2-$CH_3C_6H_4$	CH_3	F	F	F	F	O	$C_{16}H_{10}F_4N_2O$	N	8.69	8.61	172°	50
III	C_6H_5	C_2H_5	F	F	F	F	O	$C_{16}H_{10}F_4N_2O$	N	8.69	9.02	98°	60
IV	C_6H_5	C_6H_5	H	H	F	H	O	$C_{20}H_{13}FN_2O$	N	8.84	8.69	153°	58
V	2-$CH_3C_6H_4$	C_6H_5	H	H	F	H	O	$C_{21}H_{15}FN_2O$	N	8.48	8.39	118°	69
VI	2-$CH_3C_6H_4$	CH_3	H	F	H	H	O	$C_{16}H_{13}FN_2O$	N	10.45	10.32	135°	58
VII	2-$CH_3C_6H_4$	CH_3	H	H	F	H	O	$C_{16}H_{13}FN_2O$	N	10.45	10.22	138°	62
VIII	4-FC_6H_4	SH	F	F	F	F	O	$C_{14}H_7F_5N_2OS$	N	8.13	8.01	82–83°	40
IX	4-BrC_6H_4	SH	F	F	F	F	O	$C_{14}H_7BrF_4N_2OS$	N	6.93	7.03	132–134°	35
X	4-FC_6H_4	CH_2=$CHCH_2S$	F	F	F	F	O	$C_{17}H_9F_5N_2OS$	N	7.27	6.94	85–86°	95
XI	4-FC_6H_4	*n*-C_3H_7S	F	F	F	F	O	$C_{17}H_{11}F_5N_2OS$	N	7.22	7.12	69–70°	86
XII	4-BrC_6H_4	SH	F	F	F	F	S	$C_{14}H_7BrF_4N_2S_2$	N	6.65	6.68	170–172°	38

3-(4′-Bromophenyl)-5,6,7,8-tetrafluoro-2,4-quinazolinedithione (XII)—A suspension of 2-mercapto-3-(4′-bromophenyl)-5,6,7,8-tetrafluoro-4-quinazolone (2.02 g, 0.005 mole) and phosphorus pentasulfide (1.21 g, 0.006 mole) in dry xylene (10 ml) was heated under reflux with constant stirring for 4 hr. After cooling, the reaction mixture was treated with sodium carbonate solution and steam distilled to remove the xylene. The precipitated solid was separated and recrystallized from ethanol to afford a pure sample.

The IR spectra of some typical compounds are: I, 1618, 1590, and 1478–1517 cm^{-1}; II, 1610–1620, 1588, and 1480–1520 cm^{-1}; III, 1610, 1560–1590, and 1490–1520 cm^{-1}; IV, 1610, 1560–1595, and 1490–1520 cm^{-1}; and V, 1618, 1570–1590, and 1480 cm^{-1}. These absorption bands correspond to the quinazolone identifying bands (16). Similar quinazolone identifying bands were observed with the other quinazolones reported in this paper.

Biological—All compounds reported in Table I, except VIII and IX, were screened for CNS depressant activity by three tests.

Pentobarbital Sleeping Time—The method followed was similar to one used by Arora *et al.* (17). Albino mice, 24–30 g, were divided into 11 groups of four animals each. The first group received pentobarbital only (40 mg/kg ip) and served as the control group, while the other 10 groups received 10 different drugs at a dose of 100 mg/kg ip. The drugs were given 30 min prior to pentobarbital (40 mg/kg ip).

After pentobarbital administration, the stopwatch was started; as soon as the mice lost the righting reflex, they were kept on their backs separated from each other. The time from the loss of the righting reflex to the regaining of the reflex was noted as the sleeping time.

The results are given in Table II. The most potent compound was XI. Compounds IV and VII were also potent but were not as effective as XI. Compound I exhibited some activity.

Pentylenetetrazol[2] *Convulsions*—The method of Swinyard *et al.* (18) was used for the evaluation of this activity. Albino mice of either sex, 18–25 g, were randomly divided into 11 groups. Each group consisted of five animals. Group I served as the control group and was injected with an equal volume of solvent. The remaining 10 groups received the test compounds at 100 mg/kg ip. The animals were maintained on an adequate diet and were allowed free access to food and water except during the short time when they were removed from their cages for testing. The animals were tested 30 min after drug administration, since the peak effect of these compounds, determined from preliminary experiments, was between 25 and 40 min.

Seizures were induced by a subcutaneous injection of 85 mg/kg of pentylenetetrazol in agar solution. This dose produces maximal convulsions in control mice. The effectiveness of the drugs was studied by their ability to prevent the tonic phase of the seizures. Animals were observed for 30 min only after pentylenetetrazol administration.

The results of the screening data are recorded in Table III. As in the previous test, XI was the most potent anticonvulsant and IV and VII were also potent. Compounds III, IV, and XII increased the initial time for the onset of tonic phase.

Condition Avoidance Tests in Rats—The equipment employed was similar to that used by Cook and Wiedley (19). The uncondi-

[2] Metrazole.

Table II—Comparative Sleeping Times of the Screened Compounds

Compound	Mean Sleeping Time, min ± *SE*	*t*[a]	*p*
Control	21.50 ± 2.40	—	—
I	48.25 ± 5.51	4.40	<0.01
II	27.00 ± 4.20	1.20	>0.1
III	21.50 ± 3.17	0	—
IV	85.50 ± 10.96	6.30	<0.001
V	25.00 ± 2.08	1.10	>0.15
VI	29.50 ± 3.40	1.90	>0.1
VII	73.00 ± 12.87	3.90	<0.01
X	28.25 ± 1.75	2.20	>0.05
XI	100.50 ± 20.19	3.90	<0.01
XII	29.25 ± 4.13	1.60	>0.1

[a] Student *t* test.

Table III—Comparative Anticonvulsant Activity of Screened Compounds by Maximal Pentylenetetrazol Seizure Method

Group	Compound[a]	Protection, %	Mean Time for Onset of Tonic Phase, min ± *SE*	*p* for Onset of Tonic Phase
1	Control	0	11.00 ± 0.872	—
2	I	20	16.25 ± 2.27	>0.05
3	II	20	12.75 ± 1.97	>0.1
4	III	20	19.50 ± 3.03	<0.15
5	IV	40	17.33 ± 1.77	<0.01
6	V	20	13.25 ± 2.04	>0.1
7	VI	20	14.50 ± 1.32	>0.05
8	VII	60	16.00 ± 4.00	>0.1
9	X	20	15.00 ± 2.04	>0.05
10	XI	100	—	—
11	XII	20	15.00 ± 1.58	<0.05

[a] For the control group, the solvent was administered in an equal volume. All other groups received 100 mg/kg ip of the test compound.

Table IV—Comparative Condition of Avoidance Response in Rats with Screened Compounds

Group	Compound[a]	Animals Showing Absence of Conditioned Response, %
1	I	60
2	II	40
3	III	20
4	IV	80
5	V	20
6	VI	40
7	VII	80
8	X	20
9	XI	80
10	XII	40

[a] 100 mg/kg ip.

tioned response was provided to the rats through a grass stimulator (0.1 mamp of 50 cycles ac at 150 v) for 5 sec; a buzzer was used as a conditioning stimulus 12 sec earlier. Rats of either sex, 150–200 g, were trained by an electric shock to climb a pole (unconditioned response) and were then conditioned by the buzzer maintained for 15 sec to climb a pole.

Such conditioned rats were divided into 10 groups of five each. Each group received different drugs at 100 mg/kg ip. Thirty minutes after drug administration, the test was performed for observing the conditioned avoidance response.

The results of screening are recorded in Table IV; VII, XI, and IV were equally potent and I, II, VI, and XII also showed some activity.

REFERENCES

(1) W. J. Kinnard, Jr., and G. J. Carr, *J. Pharmacol. Exp. Ther.*, **121**, 354(1957).

(2) P. A. J. Janssen and A. Jagemeu, *J. Pharm. Pharmacol.*, **9**, 381(1957).

(3) J. R. Boissier and Y. F. Piccard, *Therapie*, **15**, 57(1960).

(4) S. Petersen, E. Tietze, E. Hoffmeister, and W. Wirth, British pat. 932,680 (1963).

(5) Wallace and Tiernan, Inc., British pat. 912,085 (1962).

(6) A. P. Bhaduri, N. M. Khanna, and M. L. Dhar, *J. Sci. Ind. Res.*, **21B**, 378(1962).

(7) G. Muacevic, H. Stotzer, and H. Wick, *Arzneim.-Forsch.*, **15**, 613(1965).

(8) H. C. Scarborough, U.S. pat. 3,073,826 (1963).

(9) B. V. Shetty, L. A. Companella, and E. E. Hays, U.S. pats. 3,086,910 (1963) and 3,135,659 (1964).

(10) B. Camillo and A. David, *J. Pharm. Pharmacol.*, **12**, 501(1960).

(11) C. H. Boehringer Sohn, French pat. 1,446,523; through *Chem. Abstr.*, **66**, 76030t(1968). Sumitomo Chemical Co., British pat. 1,054,718; through *Chem. Abstr.*, **66**, 76031u(1968). C. H. Boehringer Sohn, French pat. 1,446,078; through *Chem. Abstr.*, **66**, 76032v(1968).

(12) G. B. Jackman, V. Petrov, and O. Stephensen, *J. Pharm. Pharmacol.*, **12**, 529(1960).

(13) R. Hurmer and J. Vernin, British pat. 1,093,977; through *Chem. Abstr.*, **68**, 39648w(1968).

(14) K. C. Joshi and V. K. Singh, *Indian J. Chem.*, **11**, 430(1973).

(15) K. C. Joshi and V. K. Singh, *Indian J. Exp. Biol.*, **12**, 286(1974).

(16) H. Culbertson, J. C. Decius, and B. E. Christensen, *J. Amer. Chem. Soc.*, **74**, 4834(1952).

(17) R. B. Arora, M. Singh, and C. K. Arora, *Life Sci.*, **6**, 225(1962).

(18) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exp. Ther.*, **106**, 319(1952).

(19) L. Cook and E. Wiedley, *Ann. N.Y. Acad. Sci.*, **66**, 740(1957).

ACKNOWLEDGMENTS AND ADDRESSES

Received July 15, 1974, from the *Department of Chemistry, University of Rajasthan, Jaipur, India, and the ‡Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India.

Accepted for publication December 18, 1974.

The authors thank Prof. N. Ishikawa, Department of Synthetic Chemistry, Tokyo Institute of Technology, Tokyo, Japan, for providing tetrafluoroanthranilic acid, and Prof. G. B. Singh, Department of Chemistry, Banaras Hindu University, Varanasi, India, for the IR spectra and microanalysis.

‡ To whom inquiries should be directed.