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Synthesis and Isolation of New Regioisomeric 4-Thiazolidinones and Their Anticonvulsant Activity

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Two regioisomer series, 2-(3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacetylhydrazono)-3-alkyl/3-aryl-5-methyl-4-thiazolidinones (**12-21**) and 2-arylimino-3-(3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacetylamino)-5-methyl-4-thiazolidinones (**22-26**), were synthesized by the cyclization of 1-(3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacetyl)-4-alkyl/aryl thiosemicarbazides (**1-11**) with ethyl 2-bromopropionate in the presence of anhydrous sodium acetate in anhydrous ethanolic medium. The structures of **12-26** were confirmed by analytical and spectral data (IR, ^{1}H-NMR and EIMS). Selected members of the thiosemicarbazides and thiazolidinones were subjected to anticonvulsant activity tests by the National Institute of Neurological Disorders and Stroke MD, USA.

Key Words: 4-thiazolidinones, synthesis, separation, anticonvulsant activity.

Introduction

Quinazoline derivatives are used in medicine and agriculture because of their biological properties. A wide spectrum of pharmacological activity has been reported for these ligands: antimicrobial[1], anticancer[2,3], antiviral[4], anticonvulsant[5,6], antitubercular[7], and antifungal[8,9]. The sedative-hypnotic drugs methaqualon[10] and mecloqualone[11], and the diuretics phenquizone[12] and quinatozone[13] are currently used in therapy. In addition, many 4-thiazolidinones display a large variety of activities, antileukemic[14], anti-HIV[15], anticonvulsant[16,17], antimicrobial[18], etc. In view of the fact that the quinazoline ring possesses anticonvulsant properties and as part of our ongoing studies in the area of anticonvulsant agents, we synthesized some novel 2-(3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacetylhydrazono)-3-alkyl/aryl-5-methyl-4-thiazolidinones (**12-21**) and 2-arylimino-3-(3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacetylamino)-5-methyl-4-thiazolidinones (**22-26**) to screen them for anticonvulsant activities.

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Experimental

M.p.: open capillaries, Büchi 530 apparatus: uncorrected. Column chromatograpy: silica gel (70-230 mesh, Merck). IR: Perkin-Elmer 1600 for KBr pellets; cm^{-1}. ^{1}H-NMR: Bruker AC 200 and Bruker DPX 400; δ in ppm rel. to $SiMe_4$ (=0 ppm) as internal standard. EI-MS: VG Zab Spec (70 eV);m/z (rel.%). Elemental analysis: Carlo Erba 1106.

General method for the synthesis of 2-(3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacetylhydrazono)-3-methyl-5-methyl-4-thiazolidinones (12-21) and their isomers 2-phenylimino-3-(3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacetylamino)-5-methyl-4-thiazolidinones (22-26)

To a suspension of **1-11** (0.0025 mol) in 20 mL of absolute ethanol, were added anhydrous sodium acetate (0.01 mol) and 0.0025 mol ethyl 2-bromopropionate. The reaction mixture was refluxed on a water-bath for 2 h, and after cooling it was poured onto ice-cold water and allowed to stand overnight. The precipitate was filtered, then washed with water, dried and purified either by crystallization from ethanol (**12-17**) or by column chromatography employing different eluents (**18**, **22**: benzene/acetone (6:4); **19**, **20**, **23** and **24**: hexane/ethyl acetate (4:6); **21** and **25**: hexane/ethyl acetate (1:3)).

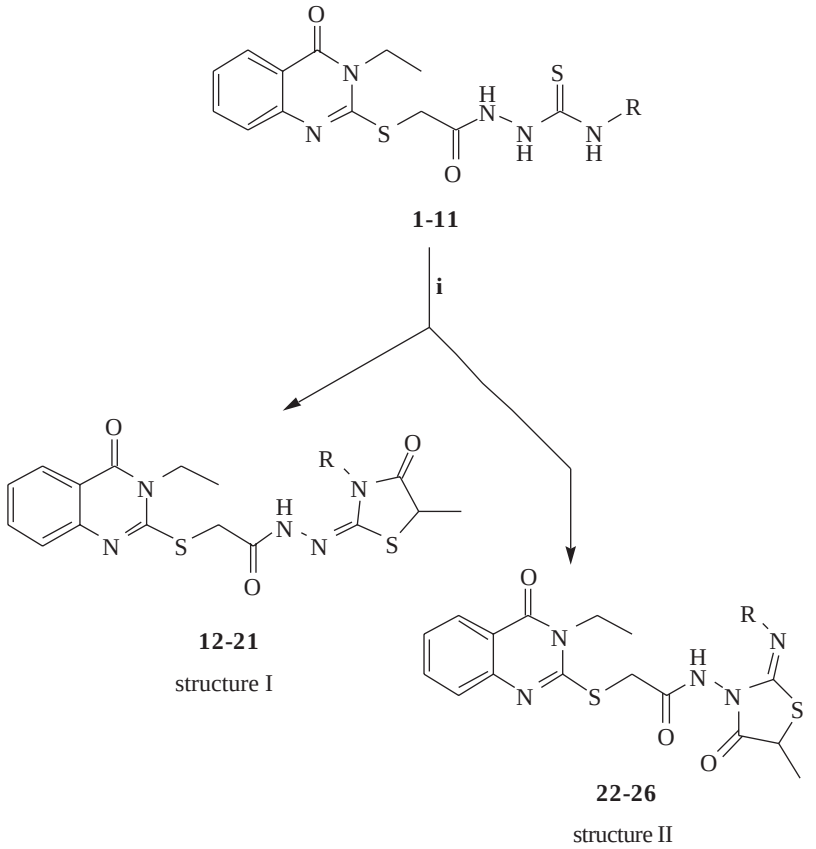
Anticonvulsant activity

The compounds to be tested were administered i.p. to Carworth Farms mice weighing 20-24.5 g in a volume of 0.01 mL/g of body weight. MES (maximal electroshock seizure): corneal electrodes primed with a drop of electrolyte solution (0.9% NaCl) were applied to the eyes and electrical stimulus (50 mA, 60 Hz) was delivered for 0.2 s at the time of peak effect of the tested compound. The animal were restrained by hand and released at the moment of stimulation in order to permit observation of the entire seizure. Abolition of the hind limb tonic-extensor component indicated that the compound can prevent MES-induced seizure spread. ScMet (subcutaneous pentetrazol seizure): the convulsant dose (CD97) of pentylenetetrazol (85 mg/kg) was injected at the time of peak effect of the test compound. The animals were isolated and observed for 30 min to see whether seizures occurred. Absence of clonic spasm persisting for at least 5 s indicated that the compound can elevate the pentylenetetrazol-induced seizure threshold. The results were expressed as number of animals protected/number of animals tested.

Results and Discussion

The synthesis of the target compounds was carried out as outlined in Scheme 1. 3-Ethyl-4(3H)-quinazolinone-2-ylmercaptoacetyl)-4-alkyl/arylthiosemicarbazides (**1-11**) were obtained by the procedures described in our previous work[19,20]. Condensation of **1-11** with ethyl 2-bromopropionate in boiling ethanol containing anhydrous sodium acetate led to the formation of regioisomers (structures I and II), 2-(3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacetylhydrazono)-3-alkyl/aryl-5-methyl-4-thiazolidinones (**12-21**) and 2-arylimino-3-(3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacetylamino)-5-methyl-4-thiazolidinones (**22-26**). In the cyclization, the key intermediate enethiol form of thiosemicarbazides is responsible for the formation of thiazolidinone[21,22]. Attempts were made to separate the obtained isomeric mixtures. Column chromatography of the structures using different eluents yielded the pure regioisomers. The structure of the regioisomers was based on our previous discussion of the structures of similar compounds[20]. Some characteristics of the

compounds are presented in Table 1.



Scheme 1. Synthesis of regioisomeric 4-thiazolidinones. **i)** $CH_3BrCHCOOEt$, CH_3COONa, abs. EtOH, 2 h.

In the IR spectra of compounds, the lactam C=O stretching of the quinazolinone ring and amide C=O stretching were observed in the 1693-1664 cm^{-1} and 1685-1649 cm^{-1} regions, respectively[19,20,23–25]. In addition to these bands, observation of a third C=O stretching band in the 1735-1712 cm^{-1} (**12-21**) and 1755-1749 cm^{-1} (**22-26**) regions was diagnostic for the thiazolidinone ring[17,20,26,27](Table 2).

^{1}H-NMR spectra of all the compounds showed the protons of the quinazolinone ring and ethyl protons in the expected regions with splitting patterns in accordance with the literature[20,23,28]. In the ^{1}H-NMR spectra of 4-thiazolidinone derivatives, the absence of the N^2-H and N^4-H of thiosemicarbazides **1-11** and the presence of new resonances attributed to the endocyclic SCHCO protons in the 4.26-4.52 ppm region provided further evidence for thiazolidinone formation[16,24,26,29]. The ^{1}H-NMR spectrum of **12-21** and **22-26** displayed the CONH proton as a singlet at 10.41-10.53 and 11.02-11.15, respectively. This difference may be explained by the resonance structures depicted in Scheme 2, which account for the relative acidity of the CONH protons of the regioisomers. Because of the different chemical environment, the CONH proton of **22-26** has higher ppm values than those of **12-21** (Table 3).

Table 1. Physical data of compounds **12-26**.

Comp.	R	Formula (M.W.)	Yield %	Rf[a)]	Mp ^{0}C	Analysis Calcd./Found C	H	N
12	CH_3	$C_{17}H_{19}N_5O_3S_2$ (405.48)	36	0.39	183-5	50.35 50.23	4.72 4.67	17.27 17.20
13	C_2H_5	$C_{18}H_{21}N_5O_3S_2$ (419.51)	97	0.55	169-72	51.53 51.32	5.04 5.04	16.69 16.71
14	C_3H_5	$C_{19}H_{21}N_5O_3S_2$ (431.52)	93	0.59	164-8	52.88 52.91	4.90 4.66	16.23 16.15
15	C_3H_7	$C_{19}H_{23}N_5O_3S_2$ (433.53)	95	0.55	178-80	52.63 52.68	5.34 5.31	16.15 16.08
16	C_6H_{11}	$C_{22}H_{27}N_5O_3S_2$ (473.6)	93	0.65	154-6	55.76 55.45	5.74 5.69	14.78 14.51
17	4-$CH_3C_6H_4$	$C_{23}H_{23}N_5O_3S_2$ (481.57)	84	0.38	198-201	57.36 57.14	4.81 4.75	14.54 14.39
18	C_6H_5	$C_{22}H_{21}N_5O_3S_2$ (467.55)	14	0.46	223-4	56.51 55.89	4.52 4.02	14.98 14.57
19	4-BrC_6H_4	$C_{22}H_{20}BrN_5O_3S_2$ (546.45)	48	0.41	229-31	48.35 47.44	3.68 3.50	12.81 12.21
20	4-ClC_6H_4	$C_{22}H_{20}ClN_5O_3S_2$ (501.99)	30	0.44	224-5	52.63 53.31	4.01 4.19	13.95 14.22
21	4-FC_6H_4	$C_{22}H_{20}FN_5O_3S_2$ (485.54)	27	0.39	210-2	54.41 54.68	4.15 4.36	14.42 14.31
22	C_6H_5	$C_{22}H_{21}N_5O_3S_2$ (467.55)	35	0.70	174-5	56.51 56.01	4.52 3.97	14.98 14.44
23	4-BrC_6H_4	$C_{22}H_{20}BrN_5O_3S_2$ (546.45)	22	0.56	181-3	48.35 47.86	3.68 3.12	12.81 12.87
24	4-ClC_6H_4	$C_{22}H_{20}ClN_5O_3S_2$ (501.99)	54	0.61	173-6	52.63 52.63	4.01 4.31	13.95 14.02
25	4-FC_6H_4	$C_{22}H_{20}FN_5O_3S_2.{}^1\!/_2H_2O$ (494.55)	42	0.57	184-6	53.42 53.37	4.28 3.41	14.16 13.89
26	4-$NO_2C_6H_4$	$C_{22}H_{20}N_6O_5S_2.{}^1\!/_2H_2O$ (521.56)	87	0.57	218-9	50.65 50.85	4.05 3.68	16.11 15.93

[a)] mobile phase on TLC: benzene/acetone (6:4)

Table 2. IR and MS spectral data of compounds **12-26**.

Comp.	IR (KBr, cm^{-1})	MS, m/z (rel. int.%)
12	3168 (NH), 1712, 1672 (C=O)	405 (M^+,3), 247 (100), 246 (11), 205 (25), 159 (12), 158 (3), 143 (1)
13	3172 (NH), 1726, 1680, 1656 (C=O)	419 (M^+,8), 248 (100), 247 (74), 246 (40), 205 (64), 173 (53), 172 (11), 157 (6)
14	3317 (NH), 1716, 1688, 1670 (C=O)	431 (M^+,3), 247 (100), 246 (13), 205 (25), 185 (5), 184 (3), 169 (6)
15	3169 (NH), 1712, 1674, 1658 (C=O)	433 (M^+,1), 247 (100), 246 (7), 205 (14), 187 (5), 186 (2), 171 (2)
16	3265 (NH), 1716, 1687, 1670 (C=O)	473 (M^+,1), 247 (100), 246 (9), 227 (2), 226 (1), 211 (1), 205 (14)
17	3204 (NH), 1727, 1685 (C=O)	481(M^+, 2), 247 (100), 246 (10), 235 (9), 234 (3), 219 (16), 205 (15)
18	3166 (NH), 1716, 1684, 1668 (C=O)	467(M^+,4), 248 (100), 247 (80), 246 (40), 221 (34), 220 (22), 205 (55)
19	3170 (NH), 1725, 1676 (C=O)	547 (M+2, 1), 545 (M^+,1), 299(301) (13,16), 298(300) (1,4), 283(285) (4,6), 247 (100), 246 (25), 205 (50)
20	3201 (NH), 1735, 1686, 1649 (C=O)	501 (M^+,1), 255(257) (7,4), 247 (100), 246 (9), 239(241) (10, 6), 205 (40)
21	3229, 3170 (NH), 1732, 1676 (C=O)	485(M^+,1), 247 (100), 246 (7), 239 (7), 238 (2), 223 (3), 205 (17)
22	3239 (NH), 1749, 1664 (C=O)	467(M^+,9), 247 (100), 246 (23), 221 (19), 220 (6), 206 (51), 205 (30)
23	3238 (NH), 1752, 1684, 1653 (C=O)	547 (M+2, 6), 545 (M^+,5), 299(301) (10,11), 298(300) (1,2), 284(286) (22,23), 247 (100), 246 (26), 205 (29)
24	3249 (NH), 1754, 1688, 1652 (C=O)	503 (M+2, 8), 501 (M^+, 18), 255(257) (20,8), 247(100), 246 (35), 240(242) (45,18), 205 (38)
25	3227 (NH), 1753, 1679, 1657 (C=O)	485(M^+,11), 247 (100), 246 (26), 239 (24), 238 (2), 224 (56), 205 (40)
26	3219 (NH), 1755, 1693, 1656 (C=O)	512(M^+,5), 266 (1), 265 (1), 251 (39), 247 (82), 246 (8), 205 (63), 63 (100)

In the EIMS, the thiazolidinone derivatives were fragmented via the routes proposed for the thiazolidinones, affording structural proof. The major fragmentation pathway involved the cleavage of the CO-NH bond, leading to fragment ions, m/z 247 that was the base peak in most of the compounds and furnishing m/z 248, m/z 246, m/z 219 and $RC_3H_4N_3OS$ (M-246), which subsequently led to fragments characteristic for the quinazolinone and thiazolidinone moieties. All compounds showed molecular ions of different intensities. In the other fragmentation route, m/z 206, m/z 205, m/z 173 and M-261 fragments were formed by the cleavage of N-N and S-CH_2 bonds and loss of sulphur[6,19,20]. In addition, the fragments of 4-thiazolidinone moiety also helped to distinguish the regioisomers. When the fragments of 4-thiazolidinone moieties were investigated, it was seen that 2-imino-4-thiazolidinones gave only isothiocyanate moiety while 2-hydrazono-4-thiazolidinones fragmented to give both isothiocyanate and isocyanate moieties. As evidence of these findings, the fragments (M+2) of the compounds **19** and **23** (4-bromophenyl derivatives) and **20** and **24** (4-chlorophenyl derivatives) were diagnostic (Scheme 3).

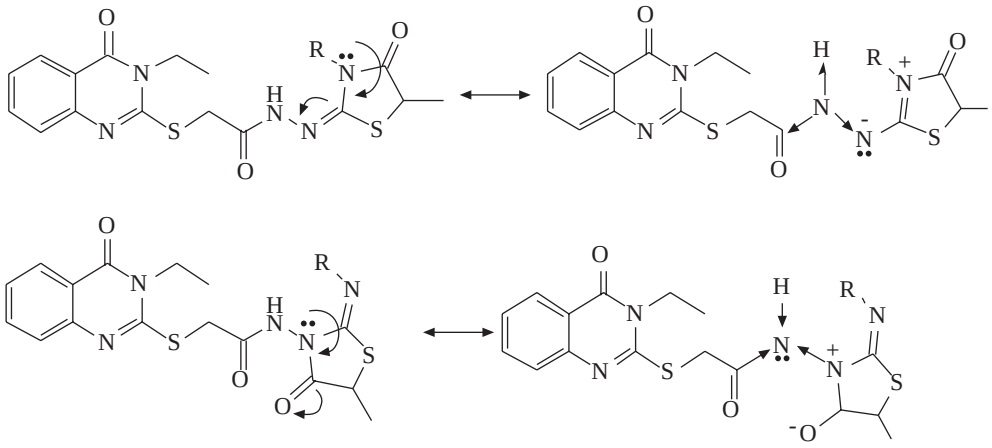
Selected members of the thiazolidinones **13** and **21** as prototypes were subjected to anticonvulsant activity tests using the maximal electroshock seizure (MES) and subcutaneous pentylenetetrazol seizure (ScMet) tests[30] by the National Institute of Neurological Disorders and Stroke MD, USA. **13** Showed low

Table 3. ^{1}H-NMR spectral data of compounds **12-26**.

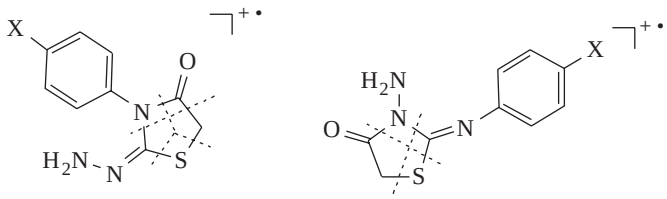
Comp.	^{1}H-NMR (DMSO-d_6, ppm)
12	1.31 (3H, t, J:7.0 Hz, NCH_2CH_3), 1.50 (3H, d, J:7.1 Hz, Th. CH_3), 3.09 (3H, s, NCH_3), 4.12 (2H, s, SCH_2), 4.13 (2H, q, J:7.1 Hz, NCH_2), 4.34 (1H, q, J:7.2 Hz, Th. SCH), 7.44 (1H, t, J:7.3 Hz, quin. C_6-H), 7.58 (1H, d, J:8.0 Hz, quin. C_8-H), 7.78 (1H, t, J:7.6 Hz, quin. C_7-H), 8.07 (1H, d, J:7.9 Hz, quin. C_5-H), 10.44 (1H, s, NH).
13	1.12 (3H, t, J:6.9 Hz, NCH_2CH_3); 1.31 (3H, t, J:7.1 Hz, NCH_2CH_3); 1.49 (3H, d, J:7.1 Hz, Th. CH_3); 3.67 (2H, q, J:6.8 Hz, NCH_2); 4.12 (2H,s, SCH_2); 4.13 (2H, q, J:7.3 Hz, NCH_2); 4.34 (1H, q, J:7.3 Hz, Th. CH); 7.44 (1H, t, J:7.6 Hz, quin. C_6-H); 7.58 (1H, d, J:7.9 Hz, quin. C_8-H); 7.78 (1H, t, J:7.6 Hz, quin. C_7-H); 8.07 (1H, dd, J:8.0, 1.0 Hz, quin. C_5-H); 10.50 (1H,s,NH).
14	1.30 (3H, t, J:7.0 Hz, NCH_2CH_3); 1.51 (3H, d, J:7.2 Hz, Th. CH_3); 4.12 (2H, s, SCH_2); 4.13 (2H, q, J:7.0 Hz, NCH_2); 4.24 (2H, d, J:4.7 Hz, CH_2-CH=); 4.38 (1H, q, J:7.1 Hz, Th. CH); 5.13 (1H, d, J:10.6 Hz, $=CH_2$); 5.21 (1H, d, J:19.2 Hz, $=CH_2$); 5.72-5.91 (1H, m, $CH=CH_2$); 7.44 (1H, t, J:7.5 Hz, quin. C_6-H); 7.57 (1H, d, J:8.1 Hz, quin. C_8-H); 7.78 (1H, t, J:7.6 Hz, quin. C_7-H); 8.07 (1H, d, J:7.8 Hz, quin. C_5-H); 10.53 (1H, s, NH).
15	0.83 (3H, t, J:7.3 Hz, $NCH_2CH_2CH_3$); 1.31 (3H, t, J:7.0 Hz, NCH_2CH_3); 1.50 (3H, d, J:7.1 Hz, Th. CH_3); 1.48-1.66 (2H, m, N-$CH_2CH_2CH_3$); 3.61 (2H, t, J:6.9 Hz, NCH_2); 4.12 (2H, s, SCH_2); 4.13 (2H, q, J:7.1 Hz, NCH_2); 4.35 (1H, q, J:7.3 Hz, Th CH); 7.44 (1H, t, J:7.5 Hz, quin. C_6-H); 7.58 (1H, d, J:8.1 Hz, quin. C_8-H); 7.78 (1H, t, J:7.4 Hz, quin. C_7-H); 8.07 (1H, d, J:7.8 Hz, quin. C_5-H); 10.48 (1H, s, NH).
16	1.03-1.34 (3H, m, cyclohex. $C_{3,4,5}$-H); 1.31 (3H, t, J:7.0 Hz, NCH_2CH_3); 1.46 (3H, d, J:7.0 Hz, Th. CH_3); 1.51-1.58 (3H, m, 3H, m, cyclohex. $C_{3,4,5}$-H); 1.73-1.79 (2H, d, 3H, m, cyclohex. $C_{2,6}$-H); 2.24-2.48 (2H, m, 3H, m, cyclohex. $C_{2,6}$-H); 4.08-4.21 (2H, m, NCH_2); 4.12 (2H, s, SCH_2); 4.08-4.32 (1H, m, 3H, m, cyclohex. C_1-H); 4.26 (1H, q, J:7.1 Hz, Th. CH); 7.44 (1H, t, J:7.5 Hz, quin. C_6-H); 7.59 (1H, d, J:8.1 Hz, quin. C_8-H); 7.78 (1H, t, J:7.2 Hz, quin. C_7-H); 8.07 (1H, d, J:7.6 Hz, quin. C_5-H); 10.46 (1H, s, NH).
17	1.28 (3H, t, J:6.9 Hz, NCH_2CH_3); 1.59 (3H, d, J:7.1 Hz, Th. CH_3); 2.33 (3H, s, CH_3); 4.08 (2H, s, SCH_2); 4.08-4.12 (2H, m, NCH_2); 4.48 (1H, q, J:6.8 Hz, Th. CH); 7.16-7.36 (4H, m, ar. H); 7.44 (1H, t, J:7.9 Hz, quin. C_6-H); 7.57 (1H, d, J:7.9 Hz, quin. C_8-H); 7.78 (1H, 2×dd, J:7.9,1.3 Hz, quin. C_7-H); 8.06 (1H, dd, J:7.9,1.1 Hz, quin. C_5-H); 10.42 (1H, s, NH).
18	1.28 (3H, t, J:6.9 Hz, NCH_2CH_3); 1.60 (3H, d, J:7.2 Hz, Th. CH_3); 4.08 (2H, s, SCH_2); 4.08-4.12 (2H, m, NCH_2); 4.50 (1H, q, J:7.1 Hz, Th. CH); 7.32 (2H, d, J:6.9 Hz, ar. H);7.41-7.52 (4H, m, quin. C_6-H and ar. H); 7.57 (1H, d, J:8.4 Hz, quin. C_8-H); 7.79 (1H, t, J:7.7 Hz, quin. C_7-H); 8.06 (1H, d, J:7.8 Hz, quin. C_5-H); 10.41 (1H, s, NH). 467 (M^+,4), 248 (100), 247 (80), 246 (40), 221 (34), 220 (22), 205 (55).
19	1.28 (3H, t, J:6.9 Hz, NCH_2CH_3); 1.60 (3H, d, J:7.1 Hz, Th. CH_3); 4.09 (2H, s, SCH_2); 4.09-4.12 (2H, m, NCH_2); 4.49 (1H, q, J:7.3 Hz, Th. CH); 7.30 (2H, d, J:7.9 Hz, ar. H); 7.44 (1H, t, J:7.8 Hz, quin. C_6-H); 7.56 (1H, d, J:8.3 Hz, quin. C_8-H); 7.67 (2H, d, J:8.5 Hz, ar. H); 7.79 (1H, t, J:7.6 Hz, quin. C_7-H); 8.06 (1H, d, J:7.9 Hz, quin. C_5-H); 10.46 (1H, s, NH).
20	1.28 (3H, t, J:6.8 Hz, NCH_2CH_3), 1.60 (3H, d, J:7.1 Hz, Th. CH_3), 4.09 (2H, s, SCH_2), 4.09-4.12 (2H, m, NCH_2), 4.50 (1H, q, J:7.1 Hz, Th. CH), 7.35-7.59 (6H, m, quin. C_6-H and ar. H), 7.79 (1H, t, J:7.40 Hz, quin. C_7-H), 8.06 (1H, d, J:7.86 Hz, quin. C_5-H), 10.51 (1H, s, NH).
21	1.28 (3H, t, J:6.7 Hz, NCH_2CH_3); 1.60 (3H, d, J:7.2 Hz, Th. CH_3); 4.08 (2H, s, SCH_2); 4.08-4.12 (2H, m, NCH_2); 4.49 (1H, q, J:6.9 Hz, Th. CH); 7.26-7.48 (5H, m, quin. C_6-H and ar. H); 7.57 (1H, d, J:8.1 Hz, quin. C_8-H); 7.78 (1H, t, J:7.5 Hz, quin. C_7-H); 8.06 (1H, d, J:7.8 Hz, quin. C_5-H); 10.50 (1H, s, NH).
22	1.30 (3H, t, J:7.0 Hz, NCH_2CH_3); 1.52 (3H, d, J:5.6 Hz, Th. CH_3); 4.12 (2H, q, J:7.0 Hz, NCH_2); 4.24 (2H, s, SCH_2); 4.44 (1H, q, Th. CH); 6.82 (2H, d, J:7.7 Hz, ar. H);7.12 (1H, t, J:7.4 Hz, ar. H); 7.31 (2H, t, J:7.6 Hz, ar. H);7.40 (1H, dd, J:8.1,1.2 Hz, quin. C_6-H); 7.54-7.67 (2H, m, quin. $C_{7,8}$-H); 8.03 (1H, d, J:7.9 Hz, quin. C_5-H); 11.04 (1H, s, NH).
23*	1.31 (3H, t, J:7.0 Hz, NCH_2CH_3); 1.54 (3H, 2×d, J:6.9,7.2 Hz, Th. CH_3); 4.12 (2H, q, J:7.1 Hz, NCH_2); 4.24 (2H, s, SCH_2); 4.45 (1H, q, Th. CH); 6.78 (2H, d, J:8.5 Hz, ar. H); 7.41 (1H, 2×dd, J:8.1 ,1.7 Hz, quin. C_6-H); 7.51 (2H, d, J:8.5 Hz, ar. H); 7.58-7.68 (2H, m, quin. $C_{7,8}$-H); 8.04 (1H, d, J:7.9 Hz, quin. C_5-H); 11.15 (1H, s, NH).
24*	1.31 (3H, t, J:7.0 Hz, NCH_2CH_3), 1.52 (3H, 2×d, J:6.9, 7.0 Hz, Th. CH_3), 4.12 (2H, q, J:7.0 Hz, NCH_2), 4.24 (2H, s, SCH_2), 4.47 (1H, q, J:7.7 Hz, Th. CH), 6.83 (2H, d, J:8.6 Hz, ar. H), 7.38 (2H, d, J:8.5 Hz, ar. H), 7.41-7.43 (1H, m, quin. C_6-H), 7.61-7.66 (2H, m, quin. $C_{7,8}$-H), 8.04 (1H, d, J:7.9 Hz, quin. C_5-H), 11.05 (1H, s, NH).
25*	1.31 (3H, t, J:7.0 Hz, NCH_2CH_3); 1.52 (3H, d, J:7.0 Hz, Th. CH_3); 4.12 (2H, q, J:7.1 Hz, NCH_2); 4.23 (2H, s, SCH_2); 4.40-4.50 (1H, m, Th. CH); 6.80 (2H, dd, J:8.8, 4.9 Hz, ar. H); 7.17 (2H, t, J:7.7 Hz, ar. H); 7.41 (1H, t, J:7.3 Hz, quin. C_6-H); 7.50-7.66 (2H, m, quin. $C_{7,8}$-H); 8.04 (1H, d, J:7.7 Hz, quin. C_5-H); 11.02 (1H, s, NH).
26	1.30 (3H, t, J:6.9 Hz, NCH_2CH_3), 1.56 (3H, s, Th. CH_3), 4.12 (2H, q, J:6.9 Hz, NCH_2), 4.24 (2H, s, SCH_2), 4.52 (1H, q, Th. CH), 7.00 (2H, d, J:8.8 Hz, ar. H), 7.33-7.41 (1H, m, quin. C_6-H), 7.59-7.61 (2H, m, quin. $C_{7,8}$-H), 8.02 (1H, d, J:7.9 Hz, quin. C_5-H), 8.19 (2H, d, J:8.8 Hz, ar. $C_{3,5}$-H), 11.12 (1H, s, NH).

*400 MHz; Th.= thiazolidinone, quin.= quinazolinone

activity and toxicity in mice (Phase 1) at doses of 100 mg/kg and 300 mg/kg. Only 4-fluorophenyl substituted thiazolidinone derivative **21** being promisingly active, showed 66% protection at 100 mg/kg.



Scheme 2. The resonance structures of the regioisomers.



Scheme 3. The proposed fragmentation of the M-246 moiety.

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