Synthesis of 5-Fluoro-2-methyl-3-(2-trifluoromethyl-1,3,4-thiadiazol-5-yl)-4(3*H*)-quinazolinone and Related Compounds with Potential Antiviral and Anticancer Activity [1]

Cyril Párkányi*, Hui Liang Yuan, Bo H. E. Strömberg [2] and Ariella Evenzahav [3]

Department of Chemistry, Florida Atlantic University,
500 N. W. 20th Street, P. O. Box 3091,
Boca Raton, FL 33431-0991

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The synthesis of ten new substituted 1,3,4-thiadiazolyl-4(3*H*)-quinazolinones **8-11**, **13**, **17**, and **20-23** is reported. Compounds **8-11** were prepared by condensation of 5-fluoro-2-methyl-3,1-benzoxazin-4-one (**3**) and 5-substituted 2-amino-1,3,4-thiadiazoles **4-7**. Compound **13** was obtained by condensation of 5-fluoro-2-methyl-3,1-benzoxazin-4-one (**3**) with DL-α-amino-ε-caprolactam (**12**). Compound **17** was synthesized by condensation of 6-bromo-2-methyl-3,1-benzoxazin-4-one (**16**) and 2-amino-5-*t*-butyl-1,3,4-thiadiazole (**5**). Compounds **20-23** were obtained by condensation of 5-chloro-6,8-dibromo-2-methyl-3,1-benzoxazin-4-one (**19**) and 5-substituted 2-amino-1,3,4-thiadiazoles **4-7**, respectively. The substituted 3,1-benzoxazin-4-ones **3**, **16**, and **19** were obtained in good yield by refluxing the appropriate anthranilic acid, **1**, **15**, and **18** with acetic anhydride (**2**).

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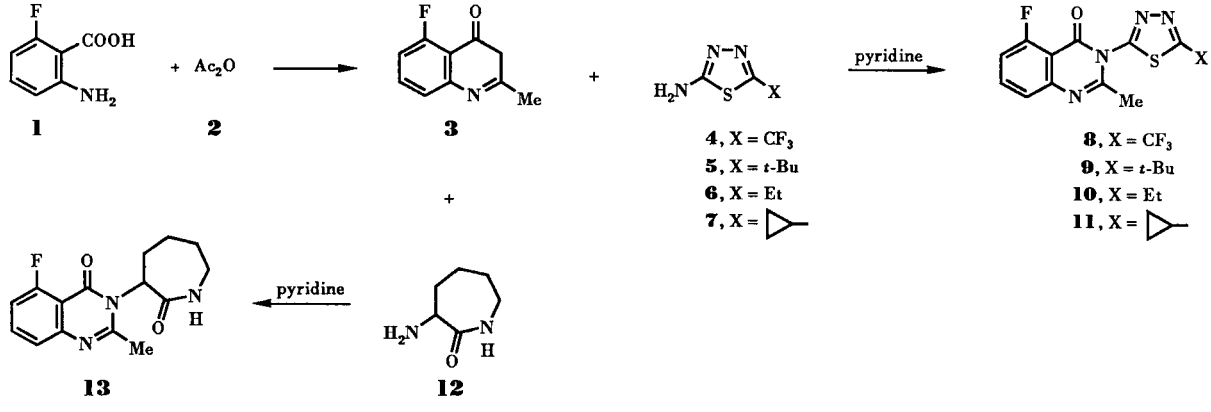
Substituted 4(3*H*)-quinazolinones are known to possess a wide range of pharmacological activities. As an example, 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone is a potent hypnotic agent, and various other derivatives possess diuretic, antihypertensive, antiinflammatory, bronchodilator, antiviral, and antitubercular activity [4-8]. It was also found that some 1,3,4-thia- and 1,3,4-selenadiazoles possess potential bactericidal properties [9]. Thus, it seemed of interest to combine the 4(3*H*)-quinazolinone system with a 1,3,4-thiadiazole ring in a single molecule as compounds of this type can be expected to be biologically active and perhaps to exhibit potential antibacterial, antiviral, and/or anticancer activity. This work represents a continuation of our systematic studies of potential antiviral and anticancer agents [10-20].

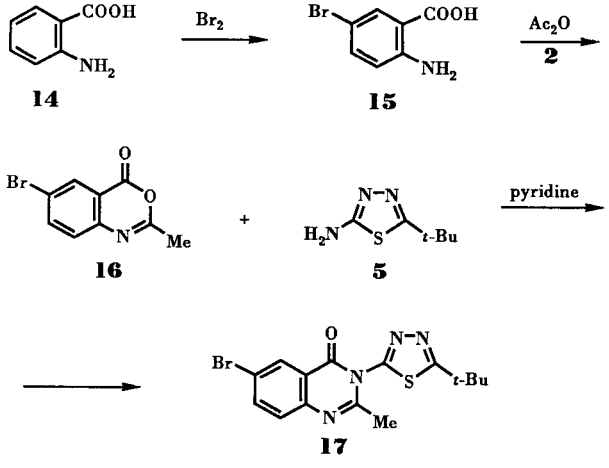
In the present contribution, we describe the synthesis of ten novel (1,3,4-thiadiazol-5-yl)-4(3*H*)-quinazolinones. The compounds were synthesized by a straightforward, two-step procedure described herein. The 5-fluoro-2-methyl-3-(2-substituted-1,3,4-thiadiazol-5-yl)-4(3*H*)-quinazolinones **8-11** were synthesized by condensation of 5-fluoro-2-methyl-3,1-benzoxazin-4-one (**3**) with 2-amino-5-trifluoromethyl-1,3,4-thiadiazole (**4**), 2-amino-5-*t*-butyl-1,3,4-thiadiazole (**5**), 2-amino-5-ethyl-1,3,4-thiadiazole (**6**), and 2-amino-5-cyclopropyl-1,3,4-thiadiazole (**7**), respectively. The needed 5-fluoro-2-methyl-3,1-benzoxazin-4-one (**3**) was obtained from 2-amino-6-fluorobenzoic acid (**1**) (Scheme 1). Condensation of **3** with DL-α-amino-ε-caprolactam (**12**) yielded 5-fluoro-2-methyl-3-(caprolactam-2-yl)-4(3*H*)-quinazolinone (**13**) (Scheme 1). 6-Bromo-2-methyl-3-(2-*t*-butyl-1,3,4-thiadiazol-5-yl)-4(3*H*)-quinazolinone (**17**) was synthesized by condensation of 6-bromo-2-methyl-3,1-benzoxazin-4-one (**16**) and 2-amino-5-*t*-butyl-1,3,4-thiadiazole (**5**). The intermediate **16** was obtained from 2-amino-5-bromobenzoic acid (5-bromoanthranilic acid, **15**) which was prepared by bromination from 2-aminobenzoic acid (anthranilic acid, **14**) (Scheme 2). The substituted 5-chloro-6,8-dibromo-2-methyl-3-(1,3,4-thiadiazol-5-yl)-4(3*H*)-quinazolinones **20-23** were prepared by condensation of 5-chloro-6,8-dibromo-3,1-benzoxazin-4-one (**19**) and the appropriate 5-substituted

Scheme 1



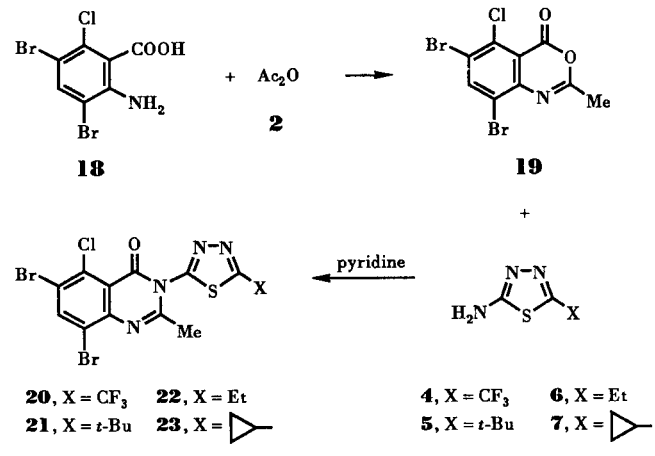
2-amino-1,3,4-thiadiazoles **4-7**, respectively. 5-Chloro-6,8-dibromo-3,1-benzoxazin-4-one (**19**) was prepared by heating of 2-amino-6-chloro-3,5-dibromobenzoic acid (**18**) with acetic anhydride (**2**) (Scheme 3).

Scheme 2



Several approaches were explored to condense the substituted benzoxazinones with 5-substituted 2-amino-1,3,4-thiadiazoles. The method of Kischer and co-workers [21] which uses a free flame for 5 minutes did not afford good yields. No improvement of the yield was observed by lengthening the reaction time. The addition of fused zinc chloride to the molten reaction mixture as suggested by Zentmyer and Wagner [22] or copper powder according to Ghosh [23] improved the yield, but the best yield was obtained by refluxing the substituted benzoxazin-4-ones and

Scheme 3



5-substituted 2-amino-1,3,4-thiadiazoles in dry pyridine for 28 hours.

The structures of the new compounds were established on the basis of their elemental microanalyses and spectral data. For example, the ir spectra of the compounds **8**, **17**, and **20** contain the characteristic C=N stretching frequencies at 1520-1560 cm^{-1} and the carbonyl group C=O stretching frequency at 1650-1700 cm^{-1}. The ^1H nmr and ^{13}C nmr spectra of the new compounds measured in dimethyl sulfoxide-d_6 (DMSO-d_6) show the presence of the expected protons, in agreement with the proposed structures. The methyl and *t*-butyl group proton signals in compound **17** appear at 1.4 and 2.0 ppm and the ^{13}C signals at 24.0 and 30.7 ppm, respectively. Complete information about the nmr, ir, and uv spectra is presented in the experimental part. All new substituted 2,3,4-thiadiazolyl-4(3*H*)-

Table 1

Substituted 5-Fluoro-2-methyl-3-(1,3,4-thiadiazol-5-yl)-4(3*H*)-quinazolinones **8-11** and **13** and 6-Bromo-2-methyl-3-(2-*t*-butyl-1,3,4-thiadiazol-5-yl)-4(3*H*)-quinazolinone **17**

Compound No.	Mp, °C (Solvent)	Yield %	Molecular Formula (mol wt)	Analysis Calcd./Found % C	H	N
8	168-170 (EtOH-H_2O, 3:1)	65	$C_{12}H_6F_4N_2OS \cdot H_2O$ (348.3)	41.38 41.28	2.31 2.12	16.09 16.01
9	206-208 (EtOH-H_2O, 5:2)	72	$C_{15}H_{15}FN_4OS \cdot H_2O$ (336.3)	53.56 53.23	5.09 4.89	16.66 16.78
10	202-204 (EtOH-H_2O, 1:1)	44	$C_{13}H_{11}FN_4OS \cdot 3/4H_2O$ (303.8)	51.39 51.41	4.14 4.10	18.44 18.64
11	184-185 (EtOH-H_2O, 3:1)	65	$C_{14}H_{11}FN_4OS$ (302.3)	55.63 55.47	3.67 4.01	18.54 [a] 18.29
13	193-194 (EtOH-H_2O, 1:1)	55	$C_{15}H_{16}FN_3O_2 \cdot H_2O$ (307.3)	58.62 59.04	5.89 5.71	13.68 13.85
17	178-180 (EtOH)	68	$C_{15}H_{15}BrN_4OS$ (379.3)	47.50 47.80	3.99 3.74	14.77 14.50

[a] S, %: 10.61/11.10.

Table 2

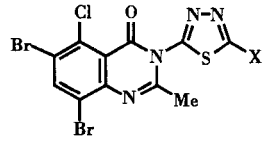
Spectral Data for Compounds **8-11, 13,** and **17**

Compound No.	^{1}H NMR Spectrum (ppm, DMSO-d_6) ^{13}C NMR Spectrum (ppm, DMSO-d_6)	IR Spectrum (cm^{-1}, potassium bromide) [a] UV Spectrum (nm (log ε), DMSO) [b]
8	CH_2, Me: 1.93; other H: 7.11, 7.33, 7.51 CH_2, Me: 23.63 other C: 111.67, 119.70, 133.10, 137.80, 150.70, 157.90 161.75, 162.90, 168.90	1690 (s, C=O), 1520 (s, C=N) 280 (4.27), 290 sh (3.97)
9	CH_2, Me: 1.34, 1.96; other H: 7.06, 7.41, 7.46 CH_2, Me: 23.58, 30.77, 35.66; other C: 111.69, 119.66, 132.17, 137.60, 158.55, 161.23, 168.71, 173.81	1700 (s, C=O), 1530 (s, C=N) 265 (3.89), 285 sh (3.84)
10	CH_2, Me: 1.28, 1.94; other H: 7.07, 7.35, 7.46 CH_2, Me: 14.10, 23.50; other C: 111.80, 116.80, 119.60, 132.20, 137.60, 158.50, 165.70, 168.70	1690 (s, C=O), 1520 (s, C=N) 285 (4.17), 295 sh (3.85)
11	CH_2, Me: 1.15, 1.94, 2.20: other H: 7.07, 7.45, 7.85 CH_2, Me: 10.41, 10.81, 23.52: other C: 111.77, 119.73, 126.67, 132.09, 137.59, 157.25, 161.59, 167.24	1710 (s, C=O), 1550 (s, C=N) 295 (4.10), 315 sh (3.72), 325 sh (3.44)
13	CH_2, Me: 1.25, 1.77, 2.11; other H: 6.91, 7.37, 8.15, 8.96 CH_2, Me: 24.45, 27.75, 28.50; other C: 110.20, 116.30, 131.20, 138.35, 162.75, 169.15, 175.60	1680 (s, C=O), 1530 (s, C=N) 290 (3.85), 304 sh (3.65)
14	CH_2, Me: 1.38, 2.00; other H: 7.65, 7.70, 8.00 CH_2, Me: 24.10, 30.75, 36.30; other C: 115.20, 124.10, 132.44, 135.20, 142.30, 148.50, 160.30, 168.80	1660 (s, C=O), 1520 (s, C=N) 268 (4.08), 309 (3.83), 336 sh (3.63)

[a] The ir spectra of compounds **8-11, 13,** and **17** exhibit broad absorption bands between 2950-3300 cm^{-1} due to C-N and C=N stretching vibrations. [b] sh indicates a shoulder.

Table 3

Substituted 5-Chloro-6,8-dibromo-1-methyl-3-(1,3,4-thiadiazol-5-yl)-4(3*H*)-quinazolinones **20-23**



Compound No.	X	Mp, °C (Solvent)	Yield %	Molecular Formula (mol wt)	Analysis Calcd. (Found)% N
20	CF_3	218-220 (EtOH-H_2O, 7:1)	56	$C_{12}H_4Br_2ClF_3N_4OS$ (504.5)	11.11 (10.95)
21	*t*-Bu	244-246 (EtOH-H_2O, 8:1)	62	$C_{15}H_{13}Br_2ClN_4OS$ (492.6)	11.38 (11.65)
22	Et	248-250 (EtOH-H_2O, 3:1)	48	$C_{13}H_9Br_2ClN_4OS$ (464.5)	12.06 (12.14) [a]
23		269-270 (EtOH-H_2O, 10:1)	55	$C_{14}H_9Br_2ClN_4OS$ (476.6)	11.76 (11.78) [b]

[a] S, %: 6.90 (7.00). [b] C, %: 35.28 (35.00); H, %: 1.90 (2.44); S, %: 6.73 (6.40).

quinazolinones and the related compounds **8-11, 13, 17,** and **20-23** will be investigated for their antiviral and antibacterial activity and the results will be reported when they become available.

Table 4

Spectral Data for Compounds **20-23**

Compound No.	^{1}H NMR Spectrum (ppm, DMSO-d_6) ^{13}C NMR Spectrum (ppm, DMSO-d_6)	IR Spectrum (cm^{-1}, potassium bromide) [a] UV Spectrum (nm (log ε), DMSO) [b]
20	CH_2, Me: 1.82; other H: 8.34 CH_2, Me: 16.90, 22.52; other C: 108.28, 123.29, 130.15, 135.55, 137.61, 157.75, 162.85, 169.02	1690 (s, C=O), 1600 (s, C=N) 314 (3.98), 325 sh (3.65)
21	CH_2, Me: 1.42, 1.88; other H: 8.30 CH_2, Me: 22.58, 30.73, 35.77; other C: 115.50, 131.49, 135.47, 137.26, 152.48, 168.49	1670 (s, C=O), 1560 (s, C=N) 295 (3.85), 305 sh (3.64)
22	CH_2, Me: 1.29, 1.88, 3.02; other H: 8.31 CH_2, Me: 14.06, 22.53, 22.95; other C: 103.55, 121.66, 130.22, 135.55, 137.29, 163.62, 168.86	1660 (s, C=O), 1550 (s, C=N) 293 (3.75), 305 sh (3.45)
23	CH_2, Me: 0.98, 1.14, 1.88, 2.47; other H: 8.31 CH_2, Me: 10.59, 22.53: other C: 105.44, 121.65, 123.58, 130.22, 135.55, 137.29, 162.00, 168.00	1660 (s, C=O), 1550 (s, C=N) 298 (3.90), 3.06 sh (3.75)

[a] The ir spectra of compounds **20-23** exhibit broad absorption bands between 2950-3300 cm^{-1} due to C-N and C=N stretching vibrations.
[b] Recorded on a Perkin-Elmer 552A spectrophotometer; sh indicates a shoulder.

EXPERIMENTAL

All melting points were determined on a Mel-Temp II capillary melting point apparatus and are uncorrected. The ^{1}H nmr and ^{13}C nmr spectra were recorded on a General Electric QE 300 (300 MHz) spectrometer. The ir spectra were measured on a Mattson Model 4020 (Galaxy) FT infrared spectrometer (intensity of the absorption: s = strong, m = medium, w = weak). The uv absorption spectra were taken on a Varian Cary 3 uv-visible spectrophotometer. The purity of all compounds was checked by thin-layer chromatography (tlc) on silica gel 60-F-254 precoated plates and the spots were located in the uv light or by iodine vapor. Elemental microanalyses were carried out by Desert Analytics, Tucson, AZ, and by the Microanalytical Laboratory of the Université d'Aix-Marseille III (Saint-Jérôme), Marseille, France. Most of the starting materials were purchased from Maybridge Chemical Company Ltd., United Kingdom. Commercial reagents were used without further purification. All solvents used were reagent grade except the dimethyl sulfoxide used for spectroscopic measurements (spectrophotometric grade).

5-Fluoro-2-methyl-3,1-benzoxazin-4-one (**3**).

2-Amino-5-fluorobenzoic acid (20 g, 0.13 mole) was refluxed with 100 ml of acetic anhydride for 30 minutes (end of the reaction was checked by tlc). The solution was cooled to room temperature and excess acetic acid was removed under reduced pressure. The resulting solid was recrystallized from cyclohexane to give light yellow crystals of **3** (19.5 g, 80%), mp 121-124°; ^{1}H nmr (DMSO-d_6): δ 2.35 (s, 3H, Me), 7.46-7.75 ppm (m, 3H, Ar); ^{13}C nmr (DMSO-d_6): δ 25.3, 31.0, 120.2, 122.8, 131.4, 134.3, 141.3, 169.9 ppm. The product was used for the synthesis of the 4-(3*H*)-quinazolinones **8-11** and **13**.

Substituted 5-Fluoro-2-methyl-3-(1,3,4-thiadiazol-5-yl)-4(3*H*)-quinazolinones **8-11** and the Related Compound **13**.

Equimolar amounts of 5-fluoro-2-methyl-3,1-benzoxazin-4-one (**3**) (0.92 g, 5 mmoles) and the appropriate 5-substituted 2-amino-1,3,4-thiadiazole **4-7** (5 mmoles) or DL-α-amino-ε-caprolactam (**12**) were thoroughly mixed and refluxed for 28 hours under anhydrous conditions in dry pyridine. The end of the reaction was checked by tlc. The pyridine was removed under reduced pressure and the residue was purified by recrystallization from a suitable solvent (with charcoal). The physical constants and spectral data for the new compounds are summarized in Tables 1 and 2.

6-Bromo-2-methyl-3,1-benzoxazin-4-one (**16**) [24-25].

2-Amino-5-bromobenzoic acid (**15**) obtained by a described procedure [26] (5.0 g, 23 mmoles) was refluxed for 40 minutes in acetic anhydride (100 ml). The solution was cooled to room temperature and excess acetic hydride was removed under reduced pressure. The residue was then purified by recrystallization from cyclohexane giving light brown crystals of **16** (4.4 g, 80%), mp 128-130° (lit mp 129-130° [27,28]).

6-Bromo-2-methyl-3-(2-*t*-butyl-1,3,4-thiadiazol-5-yl)-4(3*H*)-quinazolinone (**17**).

6-Bromo-2-methyl-3,1-benzoxazin-4-one (**16**, 0.5 g, 2 mmoles) and 2-amino-5-*t*-butyl-1,3,4-thiadiazole (**5**) (0.35 g, 2 mmoles) were refluxed in dry pyridine for 28 hours; the reaction was monitored by tlc. Upon completion, the solution was brought to room temperature, pyridine was removed under reduced pressure, and the residue was purified by recrystallization from ethanol-water (3:1) (with charcoal), mp 179-180°. The physical constants and spectral data are given in Tables 1 and 2.

5-Chloro-6,8-dibromo-2-methyl-3,1-benzoxazin-4-one (**19**).

5-Chloro-6,8-dibromo-2-methyl-3,1-benzoxazin-4-one (**19**) was synthesized in a similar fashion as compounds **3** and **16**. 2-Amino-6-chloro-3,5-dibromobenzoic acid (**18**, 5 g, 15 mmoles) was refluxed with acetic anhydride (50 ml) for 30 minutes; the solution became yellowish in color. The end of the reaction was checked by tlc. The solution was cooled to room temperature and a white precipitate was obtained. The product was filtered, washed with cold ethanol, and dried under reduced pressure giving **19** (5.2 g, 96%), mp 192-194°. This product can be used for the synthesis of the 4(3*H*)-quinazolinones without further purification.

Substituted 5-Chloro-6,8-dibromo-2-methyl-3-(1,3,4-thiadiazol-5-yl)-4(3*H*)-quinazolinones **20-23**.

5-Chloro-6,8-dibromo-2-methyl-3,1-benzoxazin-4-one (0.7 g, 2 mmoles) and a 5-substituted 2-amino-1,3,4-thiadiazole (2 mmoles) were refluxed in dry pyridine for 28 hours, with the course of the reaction checked by tlc. Pyridine was removed under reduced pressure and the residue was purified by recrystallization from a suitable solvent (with charcoal). The physical constants and spectral data of the products are listed in Tables 3 and 4.

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[2] A CHUST program participant from the School of Chemical Engineering, Royal Institute of Technology, Valhallavägen, S-100 55 Stockholm, Sweden.

[3] Present address: Department of Chemistry, Brown University, Providence, RI 02912.

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