Kurzmitteilung:

Quinazolinones, XVII[1]:

Synthesis and Pharmacological Activities of Some Antipyryloxoalkylthioquinazolinones

Chinazolinone, 17. Mitt.[1] : Synthese und pharmakologische Wirksamkeit einiger Antipyryloxoalkylthiochinazolinone

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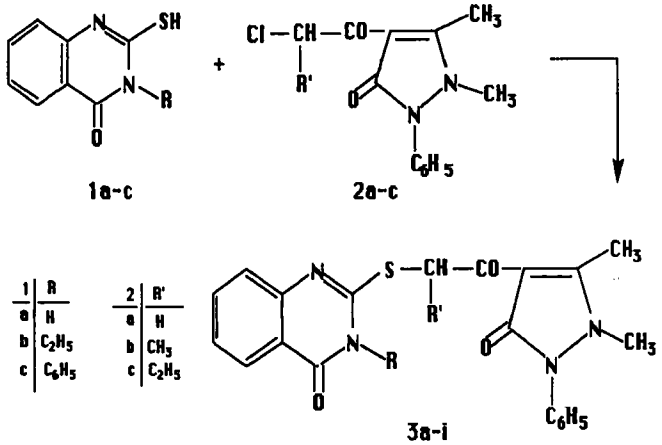
The importance of quinazolinones stems specially from their remarkable anticonvulsant, hypnotic, sedative and other activities on the central nervous system[2-6]. Besides, analgesic and antipyretic activities of antipyrine derivatives are also well known[7,8]. A synthesis of 4(3H)-quinazolinone derivative containing a rest of 4-aminoantipyrine was already described[9]. Therefore, as a continuation of our work on quinazolinones[1] it appeared interesting to prepare and to evaluate the biological potentials of new compounds obtained by incorporating these moieties in a single molecule.

Various 2-mercapto-3-substituted-4(3H)-quinazolinones **1a-c**[10] and halogenoacylantipyrines **2a-c**[11-13] were reacted in the presence of K_2CO_3 to yield the desired products **3a-i** (Scheme).

The structures of the compounds were confirmed by elemental analysis, IR-, ^{1}H-NMR-, and MS-spectrometry. Some physicochemical data are shown in Table 1.



1	R
a	H
b	C_2H_5
c	C_6H_5

2	R'
a	H
b	CH_3
c	C_2H_5

3	a	b	c	d	e	f	g	h	i
R	H	H	H	C_2H_5	C_2H_5	C_2H_5	C_6H_5	C_6H_5	C_6H_5
R'	H	CH_3	C_2H_5	H	CH_3	C_2H_5	H	CH_3	C_2H_5

Table 1: Some physicochemical data of **3a-i**

Comp.	m.p.(°C) (recr.sol.)*	Yield (%)	Molecular formula (mol.wt.)	Analysis calcd./found C	H	N	MS m/z (rel.int)
3a	226-227 (a/b)	92	$C_{21}H_{18}N_4O_3S$ (406.5)	62.1 62.1	4.46 4.34	13.8 13.7	406 (4)
3b	167-169 (a)	87	$C_{22}H_{20}N_4O_3S$ (420.5)	62.8 62.8	4.79 4.56	13.3 13.1	420 (4)
3c	241-243 (c/d)	82	$C_{23}H_{22}N_4O_3S$ (434.5)	63.6 63.4	5.10 4.95	12.9 12.8	434 (2)
3d	246 (c/a)	93	$C_{23}H_{22}N_4O_3S$ (434.5)	63.6 63.6	5.10 4.95	12.9 12.8	434 (4)
3e	169-170 (c/d)	88	$C_{24}H_{24}N_4O_3S$ (448.5)	64.3 64.1	5.39 5.51	12.5 12.3	448 (8)
3f	240-241 (c/d)	76	$C_{25}H_{26}N_4O_3S$ (462.6)	64.9 64.8	5.67 5.49	12.1 12.0	462 (2)
3g	210-211 (a)	90	$C_{27}H_{22}N_4O_3S$ .1.5H_2O (509.6)	63.6 63.5	4.95 4.99	11.0 10.6	482 (2)
3h	223-224 (a)	91	$C_{28}H_{24}N_4O_3S$ 2.H_2O (532.6)	63.1 62.9	5.29 4.95	10.5 10.7	496 (4)
3i	249-250 (a)	85	$C_{29}H_{26}N_4O_3S$ (510.6)	68.2 67.9	5.13 5.06	11.0 10.9	510 (6)

*a= ethanol, b= DMSO, c= pyridine, d= H_2O

In the IR-spectra besides aromatic and aliphatic C-H stretching bands of quinazolinone and antipyrine moieties, compounds **3a-i** show amide C=O stretching bands at 1660-1604 cm^{-1} and α,β-unsaturated ketone C=O bands at 1686-1604 cm^{-1}. In the H-NMR spectra of **3a-i** the resonance related to the C-CH_3 protons of pyrazoline ring appeared as sharp singlets between 2.57-2.61 ppm. N-CH_3 protons resonated as singlets at 3.35-3.49 ppm. The signals of the protons of the alkyl chain between quinazolinone and antipyrine nuclei were observed with expected splitting patterns and integral values. In the case of **3a-c** a singlet at 12.41-12.58 ppm attributed to quinazolinone NH group and exchangeable with D_2O was found. MS justify the structures of **3a-i**. For **3d** we could obtain the molecular-ion peak by FAB-MS.

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Table 2: Pharmacological assays performed on mice (50 mg/kg)

Compound	% Protection against pentetrazol schock	Analgesic Activity Hot plate test (score)
3a	20	1
3b	30	2
3c	20	1
3d	nil	1
3e	nil	nil
3f	nil	2
3g	nil	nil
3h	nil	nil
3i	nil	nil

The initial pharmacological screening of **3a-i** led to following results (Table 2): **3a-c** showed 20-30 % anticonvulsant activities against pentetrazol shock. **3d-i** did not exhibit a measurable activity. **3a, c, d** had low analgesic activity in hot plate test. **3b** and **3f** displayed moderate analgesic potencies at i.p. dose of 50 mg/kg. Other derivatives were devoid of any activity. The maximum anticonvulsant and analgesic activities were observed within 2.0-2.5 h after i.p. injection. **3b, c, e, f, h,** and **i** are chiral, they were tested as racemates. As they do not exhibit good activities no attempts were made to separate and to evaluate the biological potentials of their enantiomers. Weak to moderate activities of **3a-i** might be due to their different physicochemical parameters, e.g. low solubility and poor absorption in the biological medium and also to some steric and lipophilic factors.

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Experimental Part

M.p.: Büchi melting point apparatus, uncorr. - Opt. rotations (methanol): Perkin Elmer 241 MC polarimeter. - IR spectra (KBr): Perkin Elmer 1420 spectrometer. - ^{1}H-NMR spectra: Bruker WM 250 (250 MHz) spectrometer, DMSO-d_6, TMS as internal standard. - Mass spectra: Varian MAT CH 7A and Varian Mat CH5 DF spectrometers. - Elementalanalyses: Perkin Elmer elemental analyzer 240C.

General procedure for the preparation of **3a-i**

A mixture of the appropriate 2-mercapto-3-substituted-4(3H)-quinazolinone **1a-c** (5 mmol), a 4-(α-haloacyl)antipyrine derivative **2a-c** (5 mmol) and K_2CO_3 (2.5 mmol) in acetone was refluxed for 8 h. The excess acetone was evaporated i.vac.. The residue was washed with water and recrystallized from appropriate solvent (Table 1).

^{1}H-NMR data of representative compounds are as follows:

3a: 2.59 (s, 3H, C-CH_3); 3.49 (s, 3H, N-CH_3); 4.70 (s, 2H, CH_2); 7.37-8.03 (m, 9H, Ar-H).

3d: 1.31 (t, J = 7 Hz, 3H, CH_3-CH_2); 2.59 (s, 3H, C-CH_3); 3.38 (s, 3H, N-CH_3); 4.15 (q, J = 7 Hz, 2H, CH_3-CH_2); 4.78 (s, 2H, S-CH_2-); 7.31-8.07 (m, 9H, Ar-H).

3g: 2.56 (s, 3H, C-CH_3); 3.36 (s, 3H, N-CH_3); 4.65 (s, 2H, S-CH_2); 7.36-8.58 (m, 14H, Ar-H).

Anticonvulsant and analgesic activities.

Compounds **3a-i** were suspended in 5 % aqueous gum acacia. Anticonvulsant activity was screened against pentetrazol shock according[2-6]. Analgesic activity was tested and evaluated using hot plate method[14,15]. Methaqualon and acetylsalicylic acid were employed as standard substances for comparing anticonvulsant and analgesic activities. All of the pharmacological data were evaluated according to *Litchfield* and *Wilcoxon*[16].

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