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Synthesis of Some New 2-Substituted 3-[4-(N'-Arylsulphonylbiguanido)phenyl]quinazolin-4-one Hydrochlorides as Potential Anthelminthic Agents

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The title compounds **3–37** have been synthesised. Their in vivo cestodicidal activities were evaluated against *Hymenolepis nana* infection in rats. Compound **32** was found to be the most active of the series showing 81.0 % clearance of infection at a dose of 250 mg/kg for 3 days.

Synthese einiger neuer 2-substituierter 3-[4-(N'-Arylsulfonyl-biguanido)phenyl]chinazolin-4-on-Hydrochloride als potentielle Anthelminthica

Die Titelverbindungen **3–37** wurden synthetisiert und ihre anthelminthische Wirksamkeit in vivo gegen eine *Hymenolepis nana* Infektion an Ratten geprüft. Die Verbindung **32** zeigt 81.0 % Wirksamkeit im Vergleich zum Niclosamid-Standard (100 %) bei einer Dosierung von 250 mg/kg an 3 Tagen und war damit am wirksamsten.

The quinazolone nucleus have been recently reported to possess broad spectrum of antheminthic acitivity[1,2]. In addition to this, certain biguanide derivatives have also been reported to possess marked antheminthic acitivities[3]. However, so far no attempts have been made to evaluate the anthelminthic activity of compounds possessing both moieties. As a part of our programme on new anthelminthic agents[4], the present paper describes the synthesis and anthelminthic activity of 2-substituted 3-[p-(N'-arylsulphonyl-biguanido)phenyl]quinazolin-4-one hydrochlorides.

The starting material, 2-substituted-3,1-benzoxazin-4-ones **1**, were prepared by reacting the substituted anthranilic acid with different acid chlorides. Reaction of **1** with p-phenylenediamine yielded the corresponding 2-substituted phenyl-3-(p-amino phenyl)quinazolin-4-ones **2**[5–6].

The arylsulphonyldicyandiamides were prepared by reaction of arylsulphonylchloride with dicyandiamide in the presence of sodium acetate[7]. Treatment of **2** with concentrated hydrochloric acid furnished the hydrochloride of **2** which reacted smoothly with arylsulphonyldicyandiamide to afford the compounds **3–31**. Nucleophilic reaction of **31** with different cyclic amines yielded the compounds **32–37** (Scheme–1).

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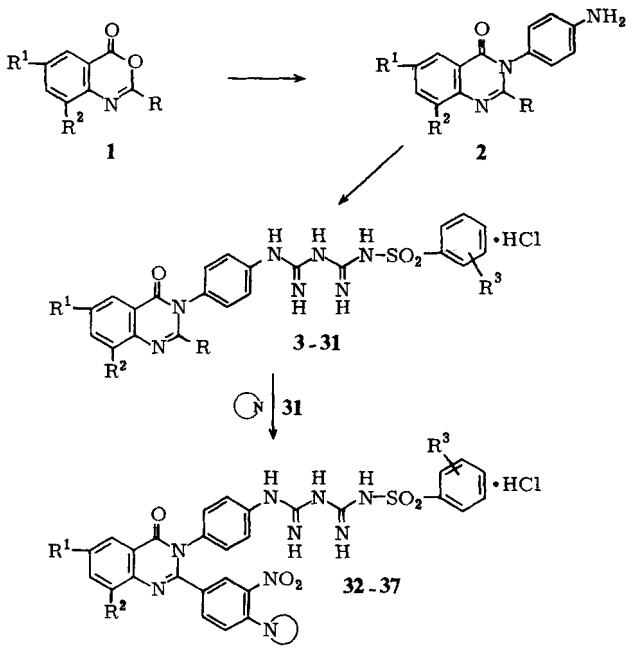

Experimental

M.P.: in H_2SO_4 bath in open capillary tubes, uncorr. *IR spectra*: Perkin-Elmer 137, 157 infracord spectrophotometer. *NMR spectra*: Varian A-60-D and Perkin-Elmer R32 spectrometers using TMS as int. ref. (chemical shifts in δ ppm). *Mass spectra*: JEOL-JMS-D300 instrument. *TLC*: Silica gel G coated plates.

2-Substituted 3-(p-N^1-arylsulphonyl-biguanido)phenyl]quinazolin-4-one hydrochlorides **3–31**

8 ml conc. HCl was added dropwise to 0.01 mol 2 substituted 3-(p-aminophenyl)quinazolin-4-one **2** at room temp. Solid 2 substituted 3-(p-aminophenyl)quinazolin-4-one hydrochloride precipitated. To the reaction mixture a stirred solution of 0.01 mole of arylsulphonyldicyandiamide in 10 ml water was added. After refluxing for 10–12 h, the resulting solution was allowed to stand overnight and the separated crystals were recrystallised from ethanol. Physical data of the compounds **3–31** are reported in Table 1.

2-[3'-nitro-4'-(N-substituted)phenyl]-3-[p-(N^1-arylsulphonylbiguanido)phenyl]quinazolin-4-one hydrochlorides **32–37**

A mixture of 8 mmole **31** and 0.01 mole heterocyclic amine in 30 ml dry pyridine was refluxed for 24 h. Solvent was removed from the reaction mixture and the residual solid obtained after washing the residue with 25 ml 2N-HCl was dried and crystallized from acetone or ethanol. The results are shown in Table 1.

Table 1: *Physical data of the compounds* **3–37**

Compound[c] No.	R^1	R^2	R^3	Molecular formula[(a)(b)]	m.p.°C	% N analyses Calcd.	Found
		R=Methyl					
3	H	H	4-OCH_3	$C_{24}H_{24}ClN_7O_4S$	252	18.1	18.0
4	H	H	4-$NHCOCH_3$	$C_{25}H_{25}ClN_8O_4S$	248	19.7	19.5
5	H	H	H	$C_{23}H_{22}ClN_7O_3S$	238	19.2	19.0
6	H	H	4-CH_3	$C_{24}H_{24}ClN_7O_3S$	226	18.6	18.5
7	H	I	H	$C_{23}H_{21}ClIN_7O_3S$	220	15.4	15.2
8	H	I	4-CH_3	$C_{24}H_{23}ClIN_7O_3S$	>280	15.0	15.0
9	H	I	4-OCH_3	$C_{24}H_{23}ClIN_7O_4S$	228	14.7	14.6
10	H	I	4-$NHCOCH_3$	$C_{25}H_{24}ClIN_8O_4S$	270	16.1	16.0
11	Br	Br	H	$C_{23}H_{20}ClBr_2N_7O_3S$	>280	14.6	14.6
12	Br	Br	4-CH_3	$C_{24}H_{22}ClBr_2N_7O_3S$	>280	14.3	14.2
13	Br	Br	4-OCH_3	$C_{24}H_{22}ClBr_2N_7O_4S$	>280	14.0	13.9
14	Br	Br	4-$NHCOCH_3$	$C_{25}H_{23}ClBr_2N_8O_4S$	268	15.4	15.3
		R=Phenyl					
15	H	Br	H	$C_{28}H_{23}ClBrN_7O_3S$	242	15.0	14.9
16	H	Br	4-CH_3	$C_{29}H_{25}ClBrN_7O_3S$	230	14.7	14.5
17	H	Br	4-$NHCOCH_3$	$C_{30}H_{26}ClBrN_8O_4S$	250	15.8	15.5
18	H	Br	4-OCH_3	$C_{29}H_{25}ClBrN_7O_4S$	>280	14.4	14.5
19	Br	Br	H	$C_{28}H_{22}ClBr_2N_7O_3S$	>280	13.4	13.2
20	Br	Br	4-CH_3	$C_{29}H_{24}ClBr_2N_7O_3S$	170	13.1	13.0
21	Br	Br	4-$NHCOCH_3$	$C_{30}H_{25}ClBr_2N_8O_4S$	240	14.2	14.0
22	Br	Br	4-OCH_3	$C_{29}H_{24}ClBr_2N_7O_4S$	>280	12.9	12.8
23	H	H	H	$C_{28}H_{24}ClN_7O_3S$	250	17.1	17.0
24	H	H	4-CH_3	$C_{29}H_{26}ClN_7O_3S$	278	16.7	16.6
25	H	H	4-$NHCOCH_3$	$C_{30}H_{27}ClN_8O_4S$	282	17.8	17.9
26	H	H	4-OCH_3	$C_{29}H_{26}ClN_7O_4S$	218	16.2	16.0
27	H	I	H	$C_{28}H_{23}ClIN_7O_3S$	238	14.0	13.9
28	H	I	4-CH_3	$C_{29}H_{25}ClIN_7O_3S$	>280	13.7	13.5
29	H	I	4-$NHCOCH_3$	$C_{30}H_{26}ClIN_8O_4S$	246	14.8	14.7
30	H	I	4-OCH_3	$C_{29}H_{25}ClIN_7O_4S$	224	13.4	13.2
	R^1=R^2=R^3=H			R =			
31				3-Nitro-4-(4′-chloro)phenyl $C_{28}H_{22}Cl_2N_8O_5S$	248	17.15	17.00
32				3-Nitro-4-(4′-methylpiperazino)phenyl $C_{33}H_{33}ClN_{10}O_5S$	210	19.53	19.40
33				3-Nitro-4-(4′-ethylpiperazino)phenyl $C_{34}H_{35}ClN_{10}O_5S$	215	19.16	19.00
34				3-Nitro-4-(piperidino)phenyl $C_{33}H_{32}ClN_9O_5S$	270	17.96	17.79
35				3-Nitro-4-(pyrrolidino)phenyl $C_{32}H_{30}ClN_9O_5S$	182	18.32	18.00
36				3-Nitro-4-(morpholino)phenyl $C_{32}H_{30}ClN_9O_6S$	222	17.91	17.72
37				3-Nitro-4-(homopiperidino)phenyl $C_{34}H_{34}ClN_9O_5S$	235	17.61	17.50

Tab. 1: (Fortsetzung)

15:	NMR(DMSO-D_6): 6.6–7.8 (m, 17H, Ar-H), 8.0–9.0 (hump, 5H, NH), Mass: M^+ at m/z = 652.
19:	NMR(DMSO-D_6): 6.5–7.7 (m, 16H, Ar-H), 7.8–8.2 (hump, 5H, NH), Mass: M^+ at m/z = 731.
23:	NMR(DMSO-D_6): 6.3–7.5 (m, 18H, Ar-H), 7.9–8.5 (hump, 5H, NH), Mass: M^+ at m/z = 573.
35:	NMR(DMSO-D_6): 1 · 63–2.0 (m, 4H, N-CH_2-$CH_2$$CH_2$), 3.30–3.55 (m, 4H, CH_2-N-CH_2), 6.7–7.6 (m, 16H, Ar-H), 8.0–8.6 (hump, 5H, NH). Mass: M^+ at m/z = 687.

(a) The elementary analyses C,H) are within the range of ± 0.4 %.

(b) The compounds were obtained in about 65 % yield.

(c) *Spectroscopic data*: IR (KBr) γ_{max} cm^{-1}: 3300–3200 (NH); 1620–1600 (>C=O); 1580–1550 (>C=N); 1350–1300 and 1160–1140 (SO_2).

Biological Assay

Determination of anthelminthic activity

The compounds were screened for their cestodicidal activity against *Hymenolepis nana* infection in rats using the technique of *Steward*[6] with slight modifications. The compounds were given orally at dosages of 500, 400 and 250 mg/kg using 3 rats per experimental group. Niclosamide was used as the standard drug in all the control experiments and it cleared 100 % of the tapeworms without scolices at a single oral dose of 50 mg/kg. The results are summarised in Table 2.

Result and Discussion

A preliminary evaluation of anticestode activity against *Hymenolepis nana* revealed that compounds **32** and **33** given at a dose of 250 mg/kg for 3 days could induce 81.0 % and 68.8 % worm expulsion in rats while compounds **16, 18–22, 26, 30–31, 37** were also found to possess 40.0–65.2 % activity at a dose of 250 mg/kg for 3 days. The rest of the screened compounds were either found inactive or showed insignificant activity at a dose of 500, 400 and 250 mg/kg.

The cestodicidal activity reported in this paper clearly demonstrates that the presence of a methyl group **(3–13)** or a substituted phenyl group **(16–37)** at R position alters activity. Introduction of a piperazine residue in **31** led to an increase of activity. Replacement of the piperazine residue by pyrrolidine **(35)** or morpholine **(36)** exhibited no change in activity but attachment of a homopiperidyl moiety **(37)** in place of the piperazine residue showed marked increase in activity. Bromine substitution at R^1 and R^2 positions leads to a better pharmacophore for the dibromo compound possesses higher activity than unsubstituted, mono bromo (R^1 = H, R^2 = Br) or iodo (R^1 = H, R^2 = I) derivatives. The percentage of inhibition of wormload observed with unsubstituted derivatives (R^3 = H) was greatly enhanced by methoxy substitution at R^3 position but the activity was selectively reduced by introduction of a methyl group in place of a methoxy group. However, slight decrease in activity was observed with an acetamido group as compared to the methyl group at R^3 position.

Tab. 2: *Cestodical activity of the compounds* 3–37

Compound No.	Cestodicidal activity against *H. nana* Dose mg/kg	% Efficacy
3	400	36.4
5	500	Inactive
6	400	10.2
7	500	Inactive
9	250	25.2
10	400	10.4
11	250	27.8
12	250	21.2
13	250	33.0
16	250	40.0
17	250	35.0
18	250	55.0
19	250	62.4
20	250	63.0
21	250	60.0
22	250	64.8
23	400	32.0
24	400	20.0
26	250	41.6
27	250	23.4
28	400	35.2
29	400	28.0
30	250	41.4
31	250	46.4
32	250	81.0
33	250	68.8
35	500	Inactive
36	500	Inactive
37	250	65.2

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