Archiv der Pharmazie

315. Band Februar 1982 Heft 2

Arch. Pharm. (Weinheim) *315*, 097–103 (1982)

Synthesis of Substituted Benzamides, Benzimidazoles and Benzoxazines as Potential Anthelmintic and Antimicrobial Agents+

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Eingegangen am 16. Februar 1981

A number of substituted benzamides **5–11**, 2,5(6)-disubstituted benzimidazoles **12–14**, 6-chloro-3-(2-nitro-5R-phenyl)-1,3-benzoxazines **15–18** and 3,8-dichloro-6-oxobenzimidazo[3,2-*a*][1,3]benzoxazine **(19)** have been synthesized. Their anthelmintic and antimicrobial activities are reported.

Synthese von substituierten Benzamiden, Benzimidazolen und Benzoxazinen als potentielle Anthelmintika und antimikrobielle Agenzien

Eine Reihe von substituierten Benzamiden **5–11**, 2,5(6)-disubstituierten Benzimidazolen **12–14**, 6-Chlor-3-(2-nitro-5R-phenyl)-1,3-benzoxazinen **15–18** und 3,8-Dichlor-6-oxobenzimidazo[3,2-a][1,3]benzoxazin **(19)** wurden synthetisiert. Sie wurden auf ihre anthelmintische und antimikrobielle Aktivität getestet.

Benzamides and benzimidazoles are extensively studied groups of compounds in the chemotherapy of intestinal helminthiasis[1,2]. However, the former has not received much attention for generating compounds active against nematodes. In continuation of our earlier efforts[3–6] to develop ideal anthelmintics, the synthesis of a series of substituted benzamides **5–11**, 2,5(6)-disubstituted benzimidazoles **12–14**, 5-substituted 6-chloro-3-(2-nitro-5-R-phenyl)-1,3-benzoxazines **15–18** and 3,8-dichloro-6-oxobenzimidazo[3,2-a][1,3]benzoxazine **(19)** have been synthesized. Their anthelmintic and their in vitro antimicrobial activity are reported in this communication.

5-(4-Methyl-1-piperazinyl)-2-nitroaniline **(2)** was made by the reaction of **1**[7] with N-methylpiperazine. Reaction of **1** with substituted salicylic acids in presence of PCl_3 gave 5-chloro-N-(5-chloro-2-nitro-phenyl)-2-hydroxybenzamide **(5)** and N-(5-chloro-2-nitro-

+ CDRI Communication No. 2807

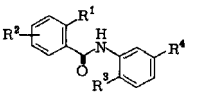


Table 1: *Physical data of substituted benzamides*

Compd. No.	R^1	R^2	R^3	R^4	Molecular formula	m.p. °C	% yield
5	OH	5-Cl	NO_2	Cl	$C_{13}H_8Cl_2N_2O_4$	185–186	60
6	OH	H	NO_2	Cl	$C_{13}H_9ClN_2O_4$	152–155	56
7	OH	5-Cl	NO_2	MP*	$C_{18}H_{19}ClN_4O_4$	130–131	77
8	OH	H	NO_2	MP	$C_{18}H_{20}N_4O_4$	205–208	50
9	H	4-NO_2	NO_2	MP	$C_{18}H_{19}N_5O_5$	183–185	83
10	H	4-NH_2	NH_2	MP	$C_{18}H_{23}N_5O$	215–216	63
11	OH	5-Cl	NH_2	Cl	$C_{13}H_{10}Cl_2N_2O_2$	> 300	70

* MP = 1-methyl-4-piperazinyl

phenyl)-2-hydroxybenzamide **(6)** resp. (Scheme 1, Table 1) which on treatment with N-methylpiperazine in boiling pyridine yielded the corresponding 4-methyl-1-piperazinyl derivatives **7–8**. N-[5-(4-Methyl-1-piperazinyl)-2-nitrophenyl]-4-nitrobenzamide **(9)** was directly prepared by refluxing a mixture of 4-nitrobenzoyl chloride and **2** in chloroform in presence of triethylamine. The benzamides **5** and **9** were hydrogenated over Raney-nickel catalyst to their corresponding amino compounds **10–11**. Cyclisation of **10–11** in presence of hydrochloric acid yielded 2-(4-aminophenyl)-5(6)-(4-methyl-1-piperazinyl)benzimidazole hydrochloride **(12)** and 5(6)-chloro-2-(5-chloro-2-hydroxyphenyl)benzimidazole hydrochloride **(13)** resp. The reaction of **12** with thiophosgene afforded 2-(4-isothiocyanatophenyl)-5(6)-(4-methyl-1-piperazinyl)benzimidazole **(14)**. The 5-substituted 6-chloro-3-(2-nitro-5R-phenyl)-2H-3,4-dihydro-1,3-benzoxazin-2-ones **15** and **17** and 2-thiones **16** and **18** were obtained by cyclization of **5** and **7** with ethyl chloroformate and thiophosgene resp. (Table 2). Treatment of **11** with thiophosgene resulted in the formation of 3,8-dichloro-6-oxobenzimidazo[3,2-a][1,3]-benzoxazine hydrochloride **(19)** (Scheme 1).

Biological Activity

Anthelmintic Activity

All the compounds have been tested against Nippostrongylus brasiliensis in rats and Nematospiroides dubius in mice by the standard methods[8,9]. The test for anticestode activity was carried out against Hymenolepis nana in mice and rats by the method of *Steward* with slight modifications[10]. The

Scheme 1

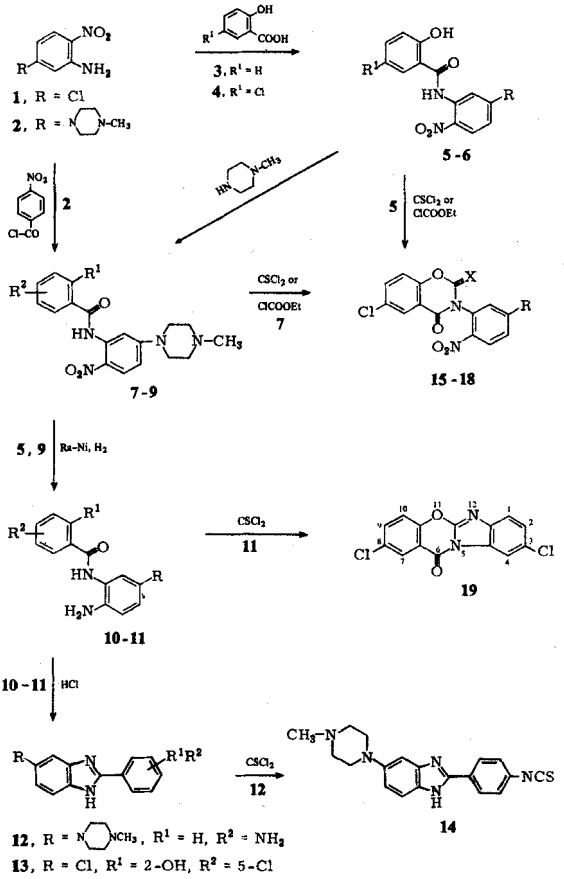
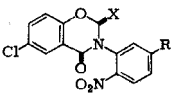


Table 2: *Physical data of 6-chloro-3-(2-nitro-5-R-phenyl)-1,3-benzoxazines*



Compd. No.	R	X	Molecular formula	M.P. °C	% Yield
15	Cl	O	$C_{14}H_6Cl_2N_2O_5$	251–252	60
16	Cl	S	$C_{14}H_6Cl_2N_2O_4S$	219–220	59
17	MP*	O	$C_{19}H_{17}ClN_4O_5$	152–153	50
18	MP	S	$C_{19}H_{17}ClSN_4O_4$	140	45

* MP = 1-methyl-4-piperazinyl

compounds were given orally at dosages 500 and 250 mg/kg daily for 3 d. In these tests all the compounds were found inactive against N. brasiliensis, N. dubius and H. nana except **5, 13, 16** and **19** which showed 86, 75, 86 and 86 % activity against N. dubius at a dose of 250 mg/kg.

Antimicrobial Activity

Some of the compounds were also evaluated for their in vitro growth inhibitory activity against the bacteriae Streptococcus faecalis, Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa and Proteus vulgaris and the fungi Candida albicans, Cryptococcus neoformans, Sporotrichum Schenckii, Trichophyton mentagrophytes and Aspergillus fumigatus by the two fold serial dilution technique[11]. None of the compounds showed antimicrobial activity up to the minimum inhibitory concentration (MIC) of 100 µg/ml except **6** which inhibited the growth of S. faecalis, K. pneumoniae, C. neoformans, S. Schenckii, T. mentagrophytes and A. fumigatus at the MICs of 12.5, 25, 50, 25, 50 and 100 µg/ml resp.

The authors thank Dr. *Nitya Anand*, Director, for his interest and encouragement in the work. Grateful thanks are due to Drs. *A.B. Sen, J.C. Katiyar* and *O.P. Srivastava* for anthelmintic and antimicrobial screenings. *ESC* and *KVBR* are thankful to UGC and CSIR, New Delhi, resp. for awarding research fellowships.

Experimental

The structures of all the compounds were checked by IR on Perkin-Elmer 157. *MS*: Jeol-JMS D300. The purity of the compounds was checked on silica gel G plates and the spots were located by iodine vapours. *MP*:in sulphuric acid bath (uncorr.). Microanalytic data of **5–19** see table 3.

5-Chloro-N-(5-chloro-2-nitrophenyl)-2-hydroxybenzamide **(5)**

4 ml (0.05 mole) of PCl_3 in 20 ml dry xylene was added dropwise to a refluxing mixture of 8.62 g (0.05 mole) 5-chlorosalicyclic acid **(4)** and 8.62 g (0.05 mole) 5-chloro-2-nitroaniline **(1)** in 100 ml xylene and refluxing continued for 2 h. 10 ml water were added gradually to the cooled reaction mixture and then xylene was removed by steam distillation. The separated solid was crystallized from ethyl acetate – tetrahydrofuran to give **5**. Yield 7.9 g (60 %), m.p. 185–186°, IR (KBr): 1315, 1570 (NO_2), 1635 (C=O), 3250 (NH), 3450 cm^{-1} (OH).

In a similar manner **6** was prepared by reacting **1** and **3**.

5-Chloro-2-hydroxy-N-[5-(4-methyl-1-piperazinyl)-2-nitrophenyl]benzamide **(7)**

A mixture of 0.6 g (5 mmole) **5** and 0.5 g (5 mmole) N-methylpiperazine in 20 ml dry pyridine was refluxed for 24 h. Pyridine was removed under reduced pressure and the residue obtained washed with 100 ml 10 % HCl. The hydrochloride was basified with ammonia, washed with water, dried and recrystallized from chloroform to yield **7**; yield 1.5 g (77 %), m.p. 130–131°; IR (KBr): 1310, 1560 (NO_2), 1645 (C=O), 3150 (NH), 3400 cm^{-1} (OH).

Using the above method **8** was obtained from **6**.

N-[5-(4-Methyl-1-piperazinyl)-2-nitrophenyl]-4-nitro-benzamide **(9)**

A mixture of 1.85 g (0.01 mole) p-nitrobenzoyl chloride, 2.36 g (0.01 mole) **2** and 1.01 g (0.01 mole) triethylamine in 20 ml chloroform was refluxed for 20 h. The cooled reaction mixture was washed with

Table 3: *Microanalytic data of compounds* **5–19**

Compd. No.	Molecular formular (M. W.)	Calcd. Found	C	H	N
5	$C_{13}H_8Cl_2N_2O_4$		47.7	2.45	8.6
	(327)		47.4	2.51	8.6
6	$C_{13}H_9ClN_2O_4$		53.3	3.08	9.6
	(292.5)		53.0	3.14	9.5
7	$C_{18}H_{19}ClN_4O_4$		55.3	4.87	14.3
	(390.5)		55.5	4.79	14.5
8	$C_{18}H_{20}N_4O_4$		60.7	5.62	15.7
	(356)		60.5	5.92	15.7
9	$C_{18}H_{19}N_5O_5$		56.1	4.93	18.2
	(385)		55.8	5.23	18.5
10	$C_{18}H_{23}N_5O$		66.5	7.08	21.5
	(325)		66.3	7.12	21.7
11	$C_{13}H_{10}Cl_2N_2O_2$		52.5	3.37	9.4
	(297)		52.3	3.45	9.2
12	$C_{18}H_{21}N_5 \cdot HCl$		62.9	6.40	20.4
	(343.5)		62.7	6.25	20.1
13	$C_{13}H_8Cl_2N_2O \cdot HCl$		49.4	2.85	8.9
	(315.5)		49.1	2.88	9.0
14	$C_{19}H_{19}N_5S$		65.3	5.44	20.1
	(349)		65.5	5.62	20.1
15	$C_{14}H_6Cl_2N_2O_5$		47.3	1.70	7.9
	(353)		47.4	1.67	7.9
16	$C_{14}H_6Cl_2N_2O_4S$		45.5	1.63	7.6
	(369)		45.2	1.42	7.7
17	$C_{19}H_{17}ClN_4O_5$		54.7	4.08	13.5
	(416.5)		54.4	4.04	13.4
18	$C_{19}H_{17}ClSN_4O_4$		52.7	3.93	13.0
	(432.5)		52.7	3.78	12.8
19	$C_{14}H_6Cl_2N_2O_2 \cdot HCl$		49.2	2.05	8.2
	(341.5)		48.9	2.14	8.3

water, dried (Na_2SO_4), concentrated and the residue crystallized from ethanol; yield 3.2 g (83 %), m.p. 183–185°, IR (KBr): 1315, 1560 (NO_2), 1670 (C=O), 3210 cm^{-1} (NH); MS: m/e = 385.

4-Amino-N-[2-amino-5-(4-methyl-1-piperazinyl)phenyl]-benzamide **(10)**

A mixture of 3.30 g (6 mmole) **9** and 0.4 g Raney-nickel in THF-ethanol was shaken under H_2 at 2.5 kg/cm^2 pressure for 6 h. The reaction mixture was filtered and the catalyst washed with ethanol. The combined filtrate was concentrated and the residue obtained passed through silica gel column using chloroform as eluant, yield 1.23 g (63 %), m.p. 215–216°. IR (KBr): 1620 (C=O), 3225 (NH), 3350, 3475 cm^{-1} (NH_2).
Using above method **11** was prepared from **5**.

5(6)-Chloro-2-(5-chloro-2-hydroxyphenyl)benzimidazole hydrochloride **(13)**

A mixture of 0.4 g (1,3 mmole) N-(2-amino-5-chlorophenyl)-5-chloro-2-hydroxybenzamide **(11)** and 30 ml 4N-HCl was refluxed for 6 h. A white solid separated on cooling. The solid was washed with water and dried to yield **13**, yield 0.31 g (73 %), m.p. 240°. IR (KBr): 1620 (C=N), 3100 (NH), 3425 cm^{-1} (OH).

In a similar manner **12** (m.p. 265–267°) was prepared from **10**.

2-(4-Isothiocyanatophenyl)-5(6)-(4-methyl-1-piperazinyl)-benzimidazole **(14)**

0.0766 ml (d = 1.5, 1 mmole) of thiophosgene was added dropwise to a stirred solution of 0.307 g (1 mmole) 2-(4-aminophenyl)-5(6)-(4-methyl-1-piperazinyl)benzimidazole hydrochloride **(12)** in 10 ml 4N-HCl at 30°. The reaction mixture was left overnight and then basified with saturated $NaHCO_3$ solution and extracted with 3 × 20 ml ethyl acetate. The organic layer was washed with water, dried (Na_2SO_4), concentrated and the residue obtained crystallized from chloroform, yield 0.25 g (71 %), m.p. 220°, IR (KBr): 2075 cm^{-1} (NCS).

3-(5-Chloro-2-nitrophenyl)-2H-3,4-dihydro-1,3-benzoxazin-2,4-dione **(15)**

A solution of 1.08 g (0.01 mole) ethyl chloroformate in 10 ml dry acetone was added dropwise to a stirred mixture of 3.27 g (0.01 mole) **5** and 1.01 g (0.01 mole) triethylamine in 20 ml dry acetone at 0°. The reaction mixture was stirred for 2 h at 30° and then refluxed for 3 h. The solvent was removed from the mixture and the residue obtained washed with water, dried and crystallized from ethanol, yield 2.12 g (60 %), m.p. 251–252°. IR (KBr): 1370, 1580 (NO_2), 1770 (N-CO-), 1805 cm^{-1} (O-CO-).

Using the above method **17** was prepared from **7**.

3-(5-Chloro-2-nitrophenyl)-4-oxo-2H-3,4-dihydro-1,3-benzoxazine-2-thione **(16)**

A solution of 0.383 ml (d = 1.5, 5 mmole) thiophosgene in 10 ml dry acetone was added dropwise at 90° to a stirred mixture of 1.63 g (5 mmole) **5** and 0.5 g (5 mmole) triethylamine in 25 ml dry acetone. The mixture was stirred for 4 h at 40° and then refluxed for 1/2 h. The solvent was removed and the residue obtained dissolved in chloroform. The chloroform solution was washed successively with water, 0.5 N-NaOH, water, dried (Na_2SO_4), concentrated and recrystallized from chloroform, yield 1.1 g (59 %), m.p. 219–220°, IR (KBr): 1320, 1525 (NO_2), 1725 cm^{-1} (C=O).

In a similar manner **18** was synthesized from **7**.

3,8-Dichloro-6-oxobenzimidazo[3,2-a][1,3]benzoxazine hydrochloride **(19)**

A solution of 383 ml (d = 1.5,5 mole) thiophosgene in 30 ml dry acetone was added dropwise to a stirred solution of 1.5 g (4.9 mmole) **11** in 30 ml dry acetone at 0°. The mixture was stirred for 3 h at 30°

and then refluxed for 3 h. The separated solid was washed with 3 × 20 ml acetone, yield 1.2 g (69 %), m.p. 222–225°. IR (KBr): 1705 (C=O) cm^{-1}.

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[Ph 387]

Arch. Pharm. (Weinheim) *315,* 103–119 (1982)

Untersuchungen an 1,3-Thiazinen, 18. Mitt.[1)]

Darstellung von 3-Amino-2-thioxo-tetrahydro-1,3-thiazin-4-onen, neuartigen cyclischen Dithiocarbazidsäureestern

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Eingegangen am 2. März 1981

3-(Thiocarbazoyl-thio)-propionsäuren **1** wurden aus Hydrazinderivaten, Schwefelkohlenstoff und β-Propiolactonen dargestellt und nach verschiedenen Methoden, überwiegend mittels Acetanhydrid unter saurer Katalyse, zu den neuartigen 3-Amino-2-thioxo-tetrahydro-1,3-thiazin-4-onen **2** cyclisiert.

1,3-Thiazines, XVIII: Preparation of 3-Amino-2-thioxotetrahydro-1,3-thiazin-4-ones, Novel Cyclic Dithiocarbazates

3-(Thiocarbazoylthio)propionic acids **1** were prepared from hydrazine derivatives, carbon disulfide and β-propiolactones. Ring closure to the novel 3-amino-2-thioxotetrahydro-1,3-thiazin-4-ones **2** was effected by different methods, mainly with acetic anhydride under acidic catalysis.