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Syntheses of Some Substituted Isatin-β-thiosemicarbazones and Isatin-β-hydrazonothiazoline Derivatives as Potential Antiviral and Antimicrobial Agents

A.-Mohsen M.E. Omar*, Nabil H. Eshba and Hassan M. Salama

Pharmaceutical Chemistry Department, Faculty of Pharmacy, University of Alexandria, Egypt
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A series of isatin-β-thiosemicarbazones and isatin-β-hydrazonothiazolines was synthesized by condensation of various isatin derivatives with N^4-substituted 3-thiosemicarbazides and cyclization of the products by phenacyl bromides. The products showed high toxicity at lower concentrations when tested for antiviral activity against MDCK cells and did not exhibit antimicrobial activity against various micro-organisms.

Synthese einiger substituierter Isatin-β-thiosemicarbazone und Isatin-β-hydrazonothiazolin-Derivate als potentielle antivirale und antimikrobielle Wirkstoffe

Eine Serie von Isatin-β-thiosemicarbazonen und Isatin-β-hydrazonothiazolinen wurde synthetisiert durch Kondensation von verschiedenen Isatin-Derivaten mit N^4-substituierten-3-thiocarbaziden und Zyklisation der Produkte mit Phenacylbromiden. In niedriger Konzentration zeigten die Verbindungen große Toxizität bei der Testung auf antivirale Wirksamkeit gegen MDCK Zellen. Es konnte keine antimikrobielle Wirkung gegen verschiedene Mikroorganismen festgestellt werden.

The discovery of the potent antiviral activity of isatin-β-thiosemicarbazone[1-3] and its N-methyl derivative (Methisazone)[4] led, in the past few decades, to extensive syntheses of related compounds and as a result, a variety of broad spectrum antiviral agents were developed. Investigation of the structure-activity relationships in a class of isatin-β-thiosemicarbazones revealed that the introduction of a chloro or methoxy function[5,6] in the 5- or 6-position of the isatin part and/or N-alkylation with simple alkyl groups[7,8] or *Mannich* bases[6,9-11] were effective in causing marked rise in activity against a

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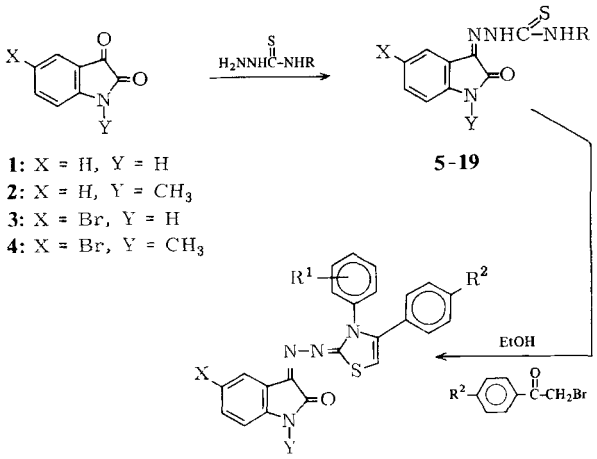
wide range of viruses and, in some cases, inducing bactericidal properties[6,9]. Likewise, the mono-[6] and disubstitution[5,12] on the nitrogen, S-alkylation[13], as well as cyclization of the thiosemicarbazone side-chain into fused heterocyclic systems, as 1,2,4-triazino[5,6-b] and [6,5-b]indoles[14–19], were efficient in increasing antiviral activities.

In view of these points, and as revealed from the recent reports claiming the production of potent antiviral[11,20] and antibacterial[21] agents when isatin was condensed with a variety of thiazolin and thiazolidin-4-ones, two novel series of isatin-β-thiosemicarbazone **5–19** and thiazoline **20–47** derivatives were synthesized (Scheme 1) to study the virucidal and bactericidal properties.



1: X = H, Y = H
2: X = H, Y = CH_3
3: X = Br, Y = H
4: X = Br, Y = CH_3

5-19

20-47

The indole-2,3-diones **1–4** were prepared in accordance with the published methods[22,23], and allowed to react with the appropriately 4-substituted 3-thiosemicarbazides in aqueous ethanol to give variously substituted isatin-β-thiosemicarbazones **5–19** (table 1). These on reaction with phenacyl bromide, the 4-bromo-, 4-chloro-, 4-nitro- or 4-methylphenacyl bromides in absolute ethanol or benzene and ethanol mixture produced the required 2-oxindole-3-(2′,3′-dihydrothiazol-2′-ylidene)hydrazone derivatives **20–47** in good yields (table 2).

The products were identified by elemental analysis (table 1 and 2), IR (exp. part) and, for some representative examples, by ^{1}H-NMR and mass spectra. The ^{1}H-NMR spectra of compounds **8, 9** and **12** showed three singlets, disappearing on deuteration, at δ = 12.78–12.85, 11.15–11.27 and 10.48–10.90 ppm for the thiosemicarbazone-N-4- and N-2-protons and the indole-NH, resp. In case of compound **10**, the singlets of the N-2-proton and the ring-NH overlapped in a broad singlet centered at δ = 10.60 ppm. The spectra of the cyclized products **20, 23, 31** and **42** lacked the downfield signals of the thiosemicarbazone protons and showed a singlet at δ = 6.44–6.73 ppm for the C-5-proton of the thiazoline ring. The mass spectrum of compound **21** showed the molecular ion peak at m/e 474 and 476 (for M+2). In accordance with the ions produced under electron impact, the molecule was found to lose carbon monoxide from the pyrroline ring to give ion **A**, at m/e 446 (448), which eliminated the substituted thiazoline part to give ion **B** at m/e

Table 1: *Isatin-β-(4-substituted)-3-thiosemicarbazones* **5–19**

Compd. No.	X	H	R	Yield %	M.P. °C Cryst. solvent	Molecular formula	Analysis % Calcd.	Found
5	H	H	C_4H_9(n)	90	199–200 A	$C_{13}H_{16}N_4OS$	C: 56.5 H: 5.8 N: 20.3 S: 11.6	56.8 6.00 20.3 11.2
6	H	H	C_6H_{11}(cyclo)	86	223–225 A	$C_{15}H_{18}N_4OS$	C: 59.6 H: 6.00 N: 18.5 S: 10.6	60.0 6.10 18.6 10.3
7	H	H	$C_6H_4CH_3$(o)	92	222–223 A	$C_{16}H_{14}N_4OS$	C: 61.9 H: 4.55 N: 18.1 S: 10.3	62.1 4.40 17.9 10.3
8	H	H	$C_6H_4CH_3$(p)	95	241–242 A	$C_{16}H_{14}N_4OS$	C: 61.9 H: 4.55 N: 18.1 S: 10.3	61.8 4.20 18.5 10.3
9	H	H	C_6H_4Br(p)	91	225–226 B	$C_{15}H_{11}BrN_4OS$	C: 48.0 H: 2.95 N: 14.9 S: 8.6	48.1 3.00 14.7 8.1
10	H	H	C_6H_4Cl(p)	96	247–248 B	$C_{15}H_{11}ClN_4OS$	C: 54.5 H: 3.35 N: 16.9 S: 9.7	54.8 3.00 16.5 9.3
11	Br	H	C_6H_5	93	254–256 B	$C_{15}H_{11}BrN_4OS$	C: 48.0 H: 2.95 N: 14.9 S: 8.6	47.8 2.80 14.8 8.9
12	Br	H	$C_6H_4CH_3$(p)	100	242–243 B	$C_{16}H_{13}BrN_4OS$	N: 14.4 S: 8.2	14.1 8.6
13	Br	H	C_6H_4Br(p)	93	239–240 B	$C_{15}H_{10}Br_2N_4OS$	C: 39.7 H: 2.22 N: 12.3 S: 7.1	39.9 2.20 11.9 6.6
14	Br	CH_3	C_6H_5	96	239–241 B	$C_{16}H_{13}BrN_4OS$	C: 49.4 H: 3.37 N: 14.4 S: 8.2	49.2 3.00 14.3 7.8

Fortsetzung Tab. 1

Compd. No.	X	H	R	Yield %	M.P. °C Cryst. solvent	Molecular formula	Analysis % Calcd.	Found
15	Br	CH_3	$C_6H_4Cl(p)$	91	241–242 B	$C_{16}H_{12}BrClN_4OS$	C: 45.4	45.1
							H: 2.85	3.1
							N: 13.2	13.5
							S: 7.6	7.2
16	H	CH_3	C_6H_5	91	222–224 B	$C_{16}H_{14}N_4OS$	C: 61.9	61.6
							H: 4.55	4.30
							N: 18.1	17.8
							S: 10.3	10.0
17	H	CH_3	$C_6H_4CH_3(p)$	94	220–222 B	$C_{17}H_{16}N_4OS$	C: 62.9	62.6
							H: 4.97	4.80
							N: 17.3	16.9
							S: 9.9	9.8
18	H	CH_3	$C_6H_4Br(p)$	89	226–227 C	$C_{16}H_{13}BrN_4OS$	C: 49.4	49.0
							H: 3.37	3.70
							N: 14.4	14.0
							S: 8.2	8.4
19	H	CH_3	$C_6H_4Cl(p)$	78	244–246 B	$C_{16}H_{13}ClN_4OS$	N: 16.3	15.9
							S: 9.3	9.2

Crystallization solvents: A = ethanol, B = n-butanol and C = dioxane.

Table 2: *1,5-Disubstituted 2-oxindole-3-(3',4'-disubstituted-2',3'-dihydrothiazol-2'-ylidene)hydrazones* **20–47**

Compd. No.	X	Y	R^1	R^2	Yield %	M.P. °C Cryst. solvent	Molecular formula	Analysis (%), Calcd./found C	H	N	S
20	H	H	H	H	66	276–277 A	$C_{23}H_{16}N_4OS$	69.7	4.07	14.1	
								69.6	4.21	14.3	
21	H	H	H	Br(p)	84	>300 A	$C_{23}H_{15}BrN_4OS$	58.1	3.18		6.7
								57.7	3.01		6.4
22	H	H	H	$NO_2(p)$	67	287–289 A	$C_{23}H_{15}N_5O_3S$	62.6	3.43		7.3
								62.8	3.86		7.7
23	H	H	$CH_3(o)$	H	83	281–282 B	$C_{24}H_{18}N_4OS$	70.2	4.42	13.7	7.8
								70.5	4.49	13.5	7.5
24	H	H	$CH_3(o)$	Br(p)	83	278–279 B	$C_{24}H_{17}BrN_4OS$			11.5	
										11.3	

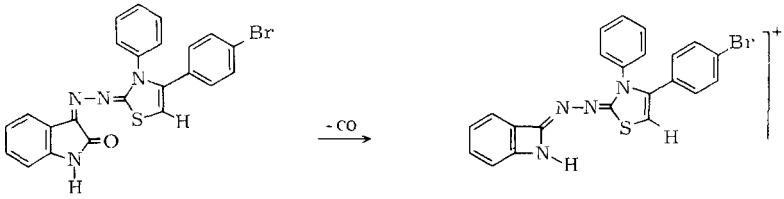
Fortsetzung Tab. 2

Compd. No.	X	Y	R^1	R^2	Yield %	M.P. °C Cryst. solvent	Molecular formula	Analysis (%), Calcd./ found C	H	N	S
25	H	H	CH_3(o)	NO_2(p)	67	291–292 C	$C_{24}H_{17}N_5O_3S$	63.3 63.6	3.76 4.10	15.4 15.3	7.0 7.4
26	H	H	CH_3(p)	H	90	272–273 B	$C_{24}H_{18}N_4OS$	70.2 70.0	4.42 4.10	13.7 13.3	
27	H	H	CH_3(p)	Br(p)	89	287–288 B	$C_{24}H_{17}BrN_4OS$	58.9 59.2	3.50 3.12	11.5 11.2	6.5 6.9
28	H	H	Br(p)	H	94	296–297 B	$C_{23}H_{15}BrN_4OS$	58.1 58.5	3.18 2.82	11.8 11.4	6.7 6.8
29	H	H	Br(p)	Br(p)	82	298–299 B	$C_{23}H_{14}Br_2N_4OS$	49.8 49.6	2.55 2.37	10.1 9.9	
30	H	H	Br(p)	CH_3(p)	96	274–275 B	$C_{24}H_{17}BrN_4OS$			11.5 11.2	6.5 6.2
31	H	H	Cl(p)	H	91	279–280 B	$C_{23}H_{15}ClN_4OS$	64.1 64.4	3.51 3.16	13.0 13.0	
32	H	H	Cl(p)	Br(p)	95	290–292 B	$C_{23}H_{14}$ – $BrClN_4OS$	54.2 54.0	2.77 2.77	11.0 10.6	6.3 5.9
33	H	H	Cl(p)	NO_2(p)	90	283–285 D	$C_{23}H_{14}ClN_5O_3S$			14.7 14.5	
34	Br	H	H	Br(p)	85	283–285 E	$C_{23}H_{14}Br_2N_4OS$	49.8 49.8	2.55 2.60	10.1 10.5	5.8 5.4
35	Br	H	H	Cl(p)	62	289–291 E	$C_{23}H_{14}BrClN_4OS$			11.0 10.9	6.3 6.0
36	Br	H	CH_3(p)	H	85	250–252	$C_{24}H_{17}BrN_4OS$			11.5 11.6	6.6 6.5
37	Br	CH_3	H	H	91	275–276 F	$C_{24}H_{17}BrN_4OS$			11.5 11.6	6.6 6.7
38	Br	CH_3	H	NO_2(p)	92	272–274 E	$C_{24}H_{16}BrN_5O_3S$			13.1 13.5	6.0 6.0
39	Br	CH_3	Cl(p)	Cl(p)	62	257–258 E	$C_{24}H_{15}BrCl_2N_4OS$			10.0 10.0	5.7 5.9
40	Br	CH_3	Cl(p)	NO_2(p)	80	260–262 E	$C_{24}H_{15}BrClN_5O_3S$			12.3 12.6	5.6 5.6

Fortsetzung Tab. 2

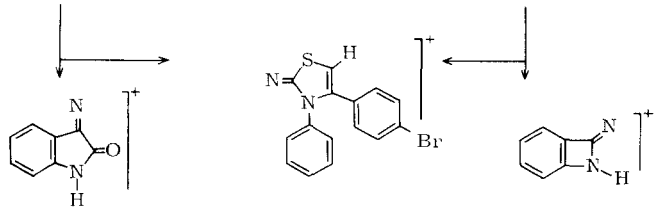
Compd. No.	X	Y	R^1	R^2	Yield %	M.P. °C Cryst. solvent	Molecular formula	Analysis (%), Calcd./ found C	H	N	S
41	H	CH_3	H	H	80	277–279 B	$C_{24}H_{18}N_4OS$			13.7 13.3	7.8 7.4
42	H	CH_3	H	CH_3(p)	77	270–272 B	$C_{25}H_{20}N_4OS$			13.2 12.9	7.6 7.2
43	H	CH_3	CH_3(p)	H	81	240–241 B	$C_{25}H_{20}N_4OS$	70.7 70.7	4.75 4.60	13.2 13.4	7.6 7.2
44	H	CH_3	CH_3(p)	Br(p)	95	253–255 E	$C_{25}H_{19}BrN_4OS$	59.6 60.0	3.80 3.45	11.1 11.4	6.4 6.7
45	H	CH_3	Br(p)	H	87	234–236 B	$C_{24}H_{17}BrN_4OS$			11.5 11.6	6.6 6.2
46	H	CH_3	Cl(p)	Cl(p)	97	267–268 E	$C_{24}H_{16}Cl_2N_4OS$	60.1 60.4	3.36 3.60	11.7 11.8	6.7 6.3
47	H	CH_3	Cl(p)	NO_2(p)	96	284–286 F	$C_{24}H_{16}ClN_5O_3S$	58.8 58.6	3.29 3.30	14.3 14.3	6.6 6.2

Crystallization solvents: A = dioxane, B = ethanol, C = dioxane/water, D = DMF/water, E = n-butanol and F = DMF



$C_{23}H_{15}BrN_4OS$
M^+: 474 (476)

A: $C_{22}H_{15}BrN_4S$
m/e 446 (448)



D: $C_8H_5N_2O$
m/e 145

C: $C_{15}H_{10}BrN_2S$
m/e 329 (331)

B: $C_7H_5N_2$
m/e 117

117. In an alternative way, compound **21** was found to be cleaved at the N-N bond of the chain to give ion **C** and **D** at m/e 329 (331) and 145, resp. The additional ions produced at lower m/e (exp. part) agreed with those reported for the cleavage of isatin[24] and similar sulfur-containing heterocyclic and open-chain systems[25,26].

Biological Screening, Results and Discussion

The products were evaluated for antiviral and antimicrobial activities in accordance with the protocol of the Drug Evaluation Branch, Chemotherapeutic Research Centre, Beecham Pharmaceuticals, Brockham Park, Betchworth, Surrey, U.K. The thiosemicarbazones **6–10** and the thiazoline derivatives **20–33** were found to be cytotoxic at < 3 μg/ml when tested for antiviral activity against MDCK cells. In addition, the products **5–47** proved to be inactive against Escherichia coli (NCTC 10418), Klebsiella aerogenes A, Pseudomonas aeruginosa (NCTC 10662), Serratia marcescenes (US 32), Staphylococcus aureus Oxford, Candida albicans (W97), Bacteroides fragilis (BC4), Bacteroides fragilis (NCTC 8560) and Bacteroides fragilis (B3).

These results reflect the effects of the various substituents introduced in the thiosemicarbazone function, although selected to have variable σ, π and Es parameters[27], and/or the bromine in the 5-position of isatin. The bulk induced by such functions as well as by the disubstituted thiazoline ring is thought to be the main factor which prevents the products from reaching the site of action and hence may explain their lack of antimicrobial activities. The presence of more than one lipophilic function[7] in the products, on the other hand, was responsible for their high toxicity against MDCK cells.

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Experimental Part

MP: not corr. *Elemental analyses*: Laboratory of Microanalysis, Faculty of Science, University of Cairo, Egypt. *^{1}H-NMR spectra*: Varian EM 360L NMR Spectrometer. *MS*: Finnigan 3200 Spectrometer.

4-Substituted isatin-β-3-thiosemicarbazones **5–19**

A mixture of isatin **(1)**, the corresponding 1-methyl- **(2)**[22], 5-bromo- **(3)** or 5-bromo-1-methyl- **(4)**[23] derivative (0.014 mole) and the equivalent amount of the 4-substituted 3-thiosemicarbazide in 50 ml 50 % aqueous ethanol was heated under reflux for 4 h. The solvent was evaporated and the products were crystallized from the proper solvents to separate as yellow to orange crystals. The yield and physical constants of the produced thiosemicarbazones **5–19** are recorded in table 1. IR (Nujol): 3320–3300, 3260–3220 and 3210–3170 (NH), 1680–160 (C=O), 1535–1520, 1335–1320, 1310–1290 and 930–925 cm^{-1} (NCS amide I, II, III and IV bands)[28]. ^{1}H-NMR for some representative products; for compound **8** (DMSO-d_6): δ (ppm) = 2.19 (s, 3H, $-CH_3$), 6.97–8.33 (m, 8H, Ar-H), 10.78 (s, 1H, indole-NH), 11.27 (s, 1H, N-2-H), 12.78 ppm (s, 1H, N-4-H); for compound **9** (DMSO-d_6) δ (ppm) = 6.96–8.33 (m, 8H, Ar-H), 10.9 (s, 1H, indole-NH), 11.3 (s, 1H, N-2-H), 12.85 ppm (s, 1H, N-4-H); for

compound **10** ($CDCl_3$/DMSO-d_6): δ (ppm) = 6.86–7.82 (m, 8H, Ar-H), 10.6 (s, broad, 2H, indole-NH and N-2-H), 12.85 ppm (s, 1H, N-4-H) and for compound **16** ($CDCl_3$/DMSO-d_6): δ (ppm) = 3.37 (s, 3H, N-CH_3), 6.96–7.92 (m, 9H, Ar-H), 10.1 (s, 1H, N-2-H) and 12.9 ppm (s, 1H, N-4-H).

1,5-Disubstituted 2-oxindole-3-(3',4'-disubstituted-2',3'-dihydrothiazol-2'-ylidene)hydrazone Derivatives **20–47**

A mixture of the isatin-β-thiosemicarbazones 5–19 (2 mmole) and 2,2 mmole) phenacyl bromide or the substituted phenacyl bromide in 25 ml absol. ethanol or a mixture of ethanol and benzene was heated under reflux for 8–15 h. The reaction mixture was concentrated and the separated orange precipitate crystallized from the proper solvents. The yield and physical constants of the produced thiazoline derivatives **20–47** are summarized in table 2. IR (Nujol): 3190–3110 (NH) and 1720–1680 cm^{-1} (C=O). ^{1}H-NMR for compound **23** (DMSO-d_6): δ (ppm) = 2.13 (s, 3H, -CH_3), 6.52–8.33 (m, 14H, Ar-H and =CH), 10.46 ppm (s, 1H, indole-NH); for compound **42** ($CDCl_3$): δ (ppm) = 2.42 (s, 3H, -CH_3), 3.27 (s, 3H, N-CH_3), 6.47 (s, 1H, =CH) and 6.7–7.84 ppm (m, 13H, Ar-H). MS for compound **21**, m/e (relative abundance %): M+2 at 476 and $M^{+\cdot}$ at 474 (100), 448 (13), 44 (13), 331 (8), 329 (8), 318 (43), 316 (62), 250 (15), 236 (7), 214 (11), 212 (10), 135 (50), 131 (26), 117 (7), 103 (39), 102 (9), 77 (92), 76 (20).

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Synthese von 5-Aryl-5,8-dihydropyrido[2,3-d]pyrimidin-2,4-diaminen

Reinhard Troschütz

Pharmazeutisches Institut der Universität Bonn, An der Immenburg 4, 5300 Bonn-Endenich
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2,4,6-Triaminopyrimidin **(2)** bildet mit 3,4,5-Trimethoxybenzyliden-1,3-dicarbonylverbindungen vom Typ **1** isolierbare *Michael*-Addukte **3**. Im sauren Milieu lassen sich die Addukte **3** leicht zu 5,8-Dihydropyrido[2,3-d]pyrimidin-diaminen **5** cyclisieren, die eine rigidisierte Trimethoprimstruktur besitzen und somit potentielle Hemmstoffe der Dihydrofolatreduktase darstellen.

Syntheses of 5-Aryl-5,8-dihydropyrido[2,3-*d*]pyrimidine-2,4-diamines

2,4,6-Triaminopyrimidine **(2)** is reacted with 3,4,5-trimethoxybenzylidene-1,3-dicarbonyl compounds of type **1** to yield the *Michael* adducts **3** which are cyclised in acidic medium to the 5,8-dihydropyrido[2,3-*d*]diamines **5**. The title compounds possess a rigid trimethoprim structure and are of interest as potential inhibitors of dihydrofolate reductase (DHFR).

Im Zusammenhang mit Synthesen von sterisch fixierten Dihydrofolatreduktasehemmern sollten Derivate des Trimethoprim (= TMP) hergestellt werden, deren Wirkung Rückschlüsse auf die Wirkkonformation von TMP und ähnlich strukturierten Dihydrofolatreduktasehemmern[1] gestatten sollte.

Zur Rigidisierung des TMP erscheinen – unter der Voraussetzung, daß die für die biologische Wirksamkeit essentielle 2,4-Diaminopyrimidinstruktur intakt bleibt – u. a. folgende beiden intramolekularen Verknüpfungen geeignet:

a) Verknüpfung von C-6 des Pyrimidinringes mit der Methylengruppe der Benzylfunktion, wodurch anellierte Pyrimidin-2,4-diamine entstehen.

b) Verknüpfung von C-6 des Pyrimidinringes mit C-2 bzw. C-6 der Benzylgruppe unter Bildung von linear kondensierten Heterocyclen mit 2,4-Diaminopyrimidinteilstruktur.

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