Monatshefte für Chemie 120, 571—574 (1989)

Monatshefte für Chemie
Chemical Monthly

Synthesis of Some Substituted Benzimidazoles with Potential Antimicrobial Activity

Ibrahim M. Labouta[1, *], **Ahmed M. M. Hassan**[1], **Omaima M. Aboulwafa**[1], and **Ola Kader**[2]

[1] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Alexandria University, Alexandria, A. R. Egypt
[2] Department of Microbiology, Medical Research Institute, Alexandria University, Alexandria, A. R. Egypt

Summary. The synthesis and *in vitro* antimicrobial evaluation of several benzimidazole derivatives with different heterocyclic nuclei at position-2 are described.

Keywords. Antimicrobial; Potential benzimidazole derivatives, synthesis and biological evaluation.

Synthese einiger substituierter Benzimidazole mit potentieller antimikrobieller Aktivität

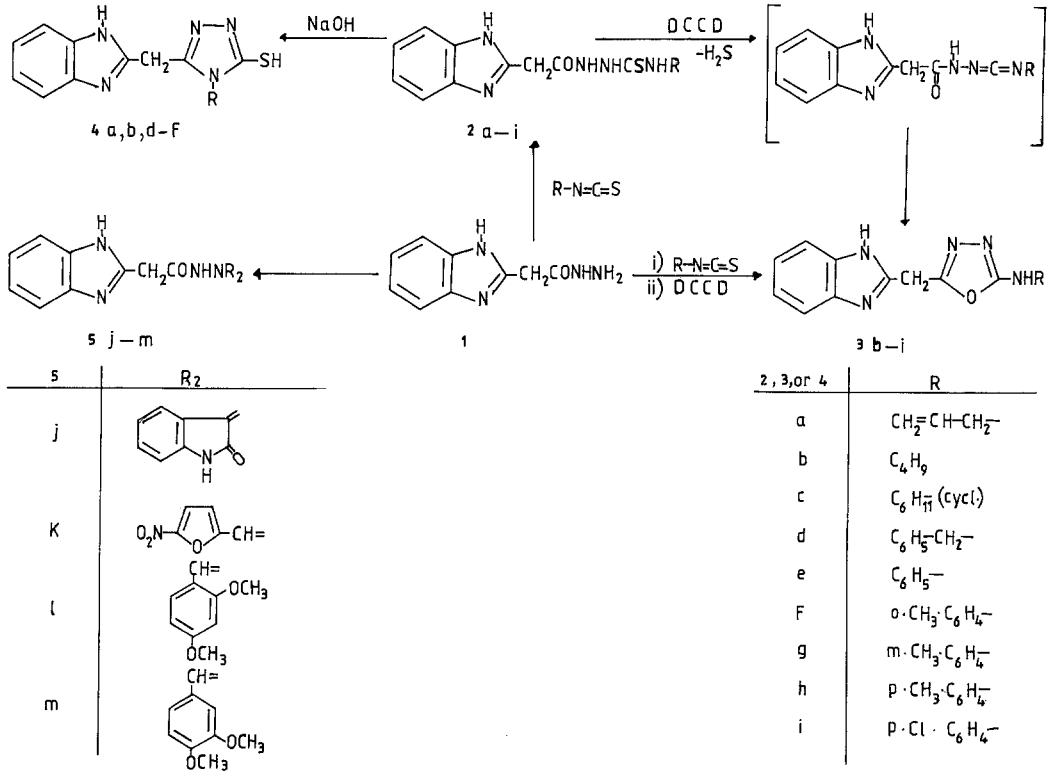
Zusammenfassung. Die Synthese und antimikrobielle Prüfung einiger Benzimidazole mit verschiedenen heterozyklischen Substituenten in 2-Stellung wird beschrieben.

Introduction

The similarity in ring structure between the benzimidazole nucleus and natural purines, hypoxanthines or guanines, made it one of the most important nuclei that has been reported to be associated with antimicrobial potency [1, 2]. Moreover, an appreciable antimicrobial activity was found to be associated with many benzimidazole derivatives carrying different heterocyclic ring systems at their 2-position [2, 3]. The introduction of a thiazolidinone nucleus to enhance the antimicrobial activity of benzimidazoles was demonstrated recently in several studies from this laboratory [4–6]. In continuation of an extensive program directed towards the synthesis of several benzimidazole derivatives, bearing at 2-position either an oxadiazole (**3 b–i**) or a triazole (**4 a**, **b**, **d–f**) nuclei, was designed. In addition, several benzimidazol-2-acethydrazones (**5 j–m**) were synthesized. The antibacterial and antifungal properties of these compounds were studied.

Results and Discussion

The synthetic sequences are given in the formula scheme (Scheme 1). The thiosemicarbazides **2 a–i** were prepared in accordance with our reported method [6]. The conversion of the latter compounds to the corresponding 2-substituted amino-



Scheme 1

5-(benzimidazol-2-ylmethyl)-1,3,4-oxadiazoles (**3b–i**, Table 1) was achieved by cyclodesulfurisation using dicyclocarbodimide (*DCCD*) in ethanol. These oxadiazoles were also obtained in a one-pot reaction by refluxing equimolar amounts of the hydrazine **1** and the selected isothiocyanate in ethanol for 30 minutes, followed by the addition of 1.5 mol *DCCD* and refluxing the mixture for 6 hours. The cyclisation of **2b–i** is assumed to proceed via a carbodiimide intermediate as previously confirmed in similar reactions [7]. The synthesis of 3-mercapto-4-substituted-5-(benzimidazol-2-ylmethyl)-1,2,4-triazoles (**4a**, **b**, **d–f**, Table 1) was accomplished by refluxing the corresponding **2a**, **b**, **d–f** with 0.1*N* sodium hydroxide. Moreover, condensation of the hydrazine **1** with the aromatic aldehydes, isatin, 5-nitrofurfuraldehyde, 2,4-dimethoxybenzaldehyde, and 3,4-dimethoxybenzaldehyde afforded the corresponding hydrazones **5j–m** (Table 2).

Antimicrobial Screening

All the new compounds were tested for their antimicrobial activity by the disc method [8], using several strains of *Escherichia coli, Staphylococcus aureus, Klebsiella aerogens, Paracolon bacilli, Proteus vulgaris,* and *Candida albicans* as the test organisms. Only compounds **5j**, **k** showed weak activity against *S. aureus* (S_{12}) as they showed inhibition zones 11 and 13 mm, respectively. Compound **5k** exhibited a MIC value at 125 µg/ml, while **5j** showed no antibacterial activity up to 500 µg/ml.

Table 1. 2-Substituted amino-5-(benzimidazol-2-ylmethyl)-1,3,4-oxadiazoles (**3b–i**) and 3-mercapto-4-substituted-5-(benzimidazol-2-ylmethyl)-1,2,4-triazoles (**4a, b, d–f**)

No.	Yield %	M.P. °C Cyrst. Solv.	Molecular Formula	Analysis (%) C	H	Calcd./Found N
	53	184–186	$C_{14}H_{17}N_5O$	61.99	6.27	25.83
3b		Benzene/Pet. ether	271.31	61.80	6.30	25.50
	56	160–163	$C_{16}H_{19}N_5O$	64.62	6.44	23.55
3c		Benzene/Pet. ether	297.35	–	–	23.30
	67	110–115	$C_{17}H_{15}N_5O$	66.87	4.95	22.94
3d		Benzene/Pet. ether	305.33	66.50	5.10	22.20
	93	216–218	$C_{16}H_{13}N_5O$	65.96	4.49	24.04
3e		*Et*OH	291.30	65.70	4.80	23.80
	74	198–200	$C_{17}H_{15}N_5O$	66.87	4.95	22.94
3f		Benzene/*Et*OH	305.33	66.00	4.60	23.30
	82	138–140	$C_{17}H_{15}N_5O$	66.87	4.95	22.94
3g		aq. *Et*OH	305.33	66.90	4.80	23.10
	85	210–212	$C_{17}H_{15}N_5O$	66.87	4.95	22.94
3h		aq. *Et*OH	305.33	66.80	4.80	22.90
	92	208–210	$C_{16}G_{12}CIN_5O$	58.94	3.71	21.50
3i		*Et*OH	325.70	58.70	3.80	21.10
	60	270–271	$C_{13}H_{13}N_5S$	57.54	4.83	25.81
4a		*Et*OH	271.20	57.70	5.10	26.00
	70	283–285	$C_{14}H_{17}N_5S$	58.50	5.96	24.37
4b			281.3	58.80	6.20	24.50
	75	256–258	$C_{17}H_{15}N_5S$	63.52	4.70	21.79
4d		*Et*OH	321.34	63.50	4.80	22.00
	80	>300	$C_{16}H_{13}N_5S$	62.51	4.26	22.79
4e		*Et*OH	307.30	62.70	4.50	23.00
	65	>300	$C_{17}H_{15}N_5S$	63.52	4.70	21.79
4f		*Et*OH	321.34	63.80	4.90	21.40

Table 2. Benzimidazol-2-acethydrazones (**5j–m**)

Comp. No.	Yield %	M.P. °C Cryst. Solv.	Molecular Formula	Analysis (%), Calcd./Found C	H	N
	70	162–170	$C_{17}H_{13}N_5O_2$	63.94	4.10	21.93
5j		*DMF*	319.31	63.94	4.10	21.80
	65	>300	$C_{14}H_{11}N_5O_4$	53.67	3.54	22.36
5k		*EtOH*	313.20	53.80	3.80	22.26
	60	190–192	$C_{18}H_{18}N_4O_3$	63.89	5.36	16.56
5i		aq. *Et*OH	338.35	63.70	5.30	16.20
	69	183–185	$C_{18}H_{18}N_4O_3$	63.89	5.36	16.56
5m		aq. *Et*OH	338.35	63.60	5.10	16.70

Experimental

All melting points are uncorrected. Infrared spectra were recorded for nujol mulls on a Beckman IR-4210 spectrophotometer. ^{1}H NMR spectra were measured on a Varian (EM 360) NMR Spectrometer, using *TMS* as an internal standard.

2-Substituted Amino-5-(benzimidazol-2-ylmethyl)-1,3,4-oxadiazoles (**3b–i**)

Method A: A solution of the appropriately substituted thiosemicarbazide **2b–i** (1 mmol) and *DCCD* (1.5 mmol) in absolute ethanol (25 ml) was heated under reflux for 6 h. Ethanol was evaporated in vacuo and the residue was dissolved in benzene and extracted with 10% hydrochloric acid (3 × 15 ml). The aqueous layer was separated and alkalised with sodium bicarbonate. The precipitated product was filtered, washed with water and crystallised from the proper solvents. IR (nujol): 3230–3190 (NH), 1640–1615 and 1515 (mixed C=N, C=C and aromatics) cm^{-1}. ^{1}H NMR (CF_3COOH) of **3g**: ξ (ppm) = 2.2 (s, 3H, CH_3), 4.9 (s, 2H, CH_2), 7.3 (s, 4H, *Ar*-H), 7.5–7.85 (m, 4H, *Ar*-H); for **3i** (CF_3COOH): ξ (ppm) = 5.1 (s, 2H, CH_2), 7.2–7.85 (m, 8H, *Ar*-H).

Method B: A solution of **1** (0.6 g; 3 mmol) and the proper isothiocyanate (3 mmol) in absolute ethanol (30 ml) was heated under reflux for 30 min. *DCCD* (0.95 g, 4.6 mmol) was then added and the mixture heated for 6 h. The cooled reaction mixture was then worked up as described under method A.

3-Mercapto-4-substituted-5-(benzimidazol-2-ylmethyl)-1,2,4-triazoles (**4a, b, d–f**)

A solution of the proper **2a, b, d–f** (10 mmol) in sodium hydroxide solution (150 ml, 0.1 *N*) was refluxed for 2 h. After cooling, the *pH* was adjusted to 6–7 using hydrochloric acid solution (0.1 *N*). The product that separated out was filtered and crystallised from the proper solvents. IR (nujol): 3210–3100 (NH); 2600 (−SH); 1620–1595, 1585–1575, 1495–1485 (mixed C=N, C=C and aromatics); 1505 and 1335–1325 (2-substituted benzimidazole) [9], and a weak band at 1250–1225 (C=S) cm^{-1}. ^{1}H NMR (CF_3COOH) of **4a**: ξ (ppm) = 4.85 (broad s, 2H, $-CH_2-CH=CH_2$), 4.90 (s, 2H, $-CH_2$), 5.1–5.9 (m, 3H, $-CH=CH_2$), 7.35–7.90 (m, 4H, *Ar*–H); for **4f** (CF_3-COOH): ξ (ppm) = 2.1 (s, 3H, CH_3), 4.55 (s, 2H, CH_2), 7.1–7.75 (m, 8H, *Ar*–H).

Benzimidazol-2-acethydrazones (**5j–m**)

A solution of **1** (1 g, 5 mmol) and the appropriate aldehyde (5 mmol) in ethanol (20 ml) was heated under reflux for 3 h, then diluted with water. The precipitated product was filtered and recrystallised from the proper solvents. IR (nujol): 3300–3180 (NH); 1650–1635 (amide II); 1620–1590, 1585–1570, 1505–1495 (mixed C=N, C=C and aromatics) cm^{-1}.

References

[1] Preston P. N. (1974) Chem. Rev. **74**: 279
[2] Brown F. C. (1961) Chem. Rev. **61**: 463
[3] Singh S. P., Parmar S. S., Raman K., Stenberg V. I. (1981) Chem. Rev. **81**: 175
[4] Rida S. M., Salama H. M., Labouta I. M., A-Ghany Y. S. (1985) Pharmazie **40**: 727
[5] Rida S. M., Salama H. M., Labouta I. M., A-Ghany Y. S. (1986) Pharmazie **41**: 324
[6] Rida S. M., Labouta I. M., Salama H. M., A-Ghany Y. S., El-Ghazzawi E., Kader O. (1986) Pharmazie **41**: 475
[7] Omar M. A., Habib N. S., Aboulwafa O. M. (1977) Synthesis: 864
[8] Baver A. W., Kirby W. M. M., Sherris J. C., Turck M. (1966) A. J. Clin. Path. **45**: 439
[9] Rabiger D. J., Joullie N. M. (1964) J. Org. Chem. **29**: 476

Received August 16, 1988. Accepted September 16, 1988