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On the Synthesis of Pyrazino[2,3-*b*]phenazine and 1*H*-Imidazo[4,5-*b*]phenazine Derivatives

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Summary. Several pyrazino[2,3-*b*]phenazine derivatives were prepared by the reaction of 2,3-diaminophenazine with different 1,2-diketones. Nucleophilic substitution of 2,3-dibromomethyl-pyrazino[2,3-*b*]phenazine with propanol, morpholine, and potassium thiocyanate gave 2,3-*bis*-(propoxymethyl)-pyrazino[2,3-*b*]phenazine, 2,3-*bis*-(4-morpholinylmethyl)-pyrazino[2,3-*b*]phenazine, and 2,3-*bis*-(cyanosulfanylmethyl)-pyrazino[2,3-*b*]phenazine. 2-Aryl-1*H*-imidazo[4,5-*b*]phenazine derivatives were synthesized by a one-pot reaction of 2,3-diaminophenazine with different aromatic aldehydes or acids. Reaction of 2,3-diaminophenazine with acetic anhydride and formic acid afforded 1*H*-imidazo[4,5-*b*]phenazine and 2-methyl-1*H*-imidazo[4,5-*b*]phenazine. Chemical and spectroscopic evidences for the product structures of the new compounds are presented.

Keywords. Diketone; Condensation; Substitution; Phenazine; Imidazole.

Zur Synthese von Pyrazino[2,3-*b*]phenazin- und 1*H*-Imidazo[4,5-*b*]phenazinderivaten

Zusammenfassung. Einige Pyrazino[2,3-*b*]phenazinderivate wurden durch Reaktion von 2,3-Diaminophenazin mit verschiedenen 1,2-Diketonen dargestellt. Nucleophile Substitution von 2,3-Dibrommethyl-pyrazino[2,3-*b*]phenazin mit Propanol, Morpholin und Kaliumthiocyanat ergab 2,3-*Bis*(propoxymethyl)-pyrazino[2,3-*b*]phenazin, 2,3-*Bis*-(4-morpholinylmethyl)-pyrazino[2,3-*b*]phenazin und 2,3-*Bis*-(cyanosulfanylmethyl)-pyrazino[2,3-*b*]phenazin. 2-Aryl-1*H*-imidazo[4,5-*b*]phenazinderivate wurden in einer Eintopfreaktion aus 2,3-Diaminophenazin mit verschiedenen aromatischen Aldehyden oder Carbonsäuren hergestellt. Reaktion von 2,3-Diaminophenazin mit Essigsäureanhydrid oder Ameisensäure lieferte 1*H*-Imidazo[4,5-*b*]phenazin und 2-Methyl-1*H*-imidazo[4,5-*b*]phenazin. Chemische und spektroskopische Nachweise für die Struktruren der neuen Verbindungen werden mitgeteilt.

Introduction

A number of phenazines have demonstrated a broad spectrum of significant biological properties [1–6], *i.e.* antibacterial [7], antifungicidal [8], antitumor [9], antibiotic [10], antihypoxic, antileprosy, and anthelmintic activity [11]. They inhibit metalloenzymes, and halosubstituted phenazines are useful as herbicides

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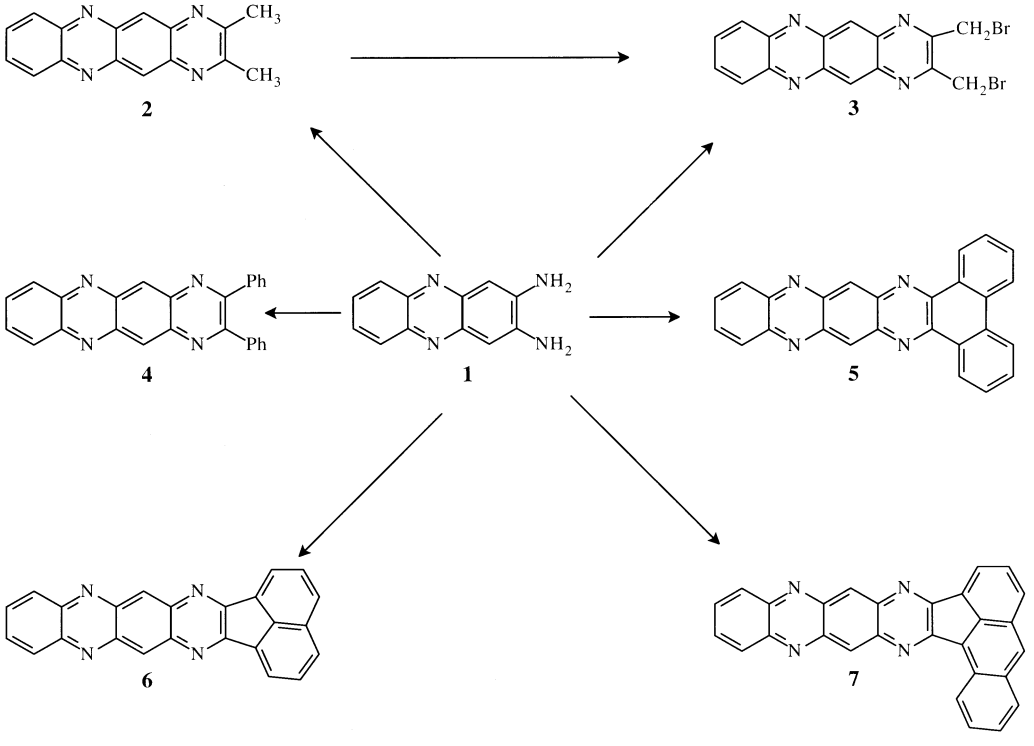
[12]. In recent years, semi- and photoconductivity has been reported for several aza aromatic compounds [13–17]. In the course of a program on the synthesis of new heterocyclic systems derived from phenazines for studying their utility as pharmacological and photoconductive agents, we report the preparation of a number of pyrazino[2,3-*b*]phenazines and imidazo[4,5-*b*]phenazines.

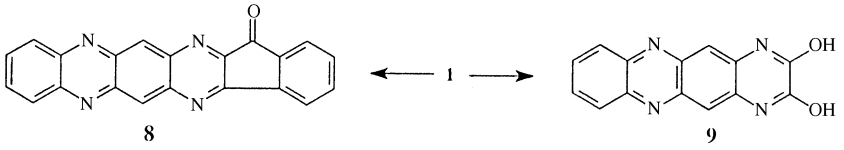
Results and Discussion

o-Diamino groups on aromatic rings have attracted considerable interest as potential building blocks for many nitrogen containing heterocyclic systems. The present work was focused on the synthesis of new series of fused phenazine aystems. The condensation reaction of 2,3-diamino-phenazine (**1**) with appropriate 1,2-diketones (butane-2,3-dione, 1,4-dibromobutane-2,3-dione, benzil, phenanthrenequinone, acenaphthenequinone, and aceanthrenequinone) were carried out in the presence of acetic acid under reflux to give the corresponding cyclic products **2–7** (Scheme 1). Compounds **3** could be also obtained in low yield from **2** and N-bromosuccinimide. Similarly, the condensation of **1** with ninhydrin was carried out in the same manner as the former reaction affording the hexacyclic compound **8**. Treatment of **1** with oxalyl chloride in boiling pyridine gave **9** (Scheme 2).

The 2,3-dibromomethyl derivative **3**, however, was very unstable in the presence of base or nucleophile. Addition of pyridine to **3** immediately gave a red solution which turned dark brown within minutes. We ascribe the base sensitivity

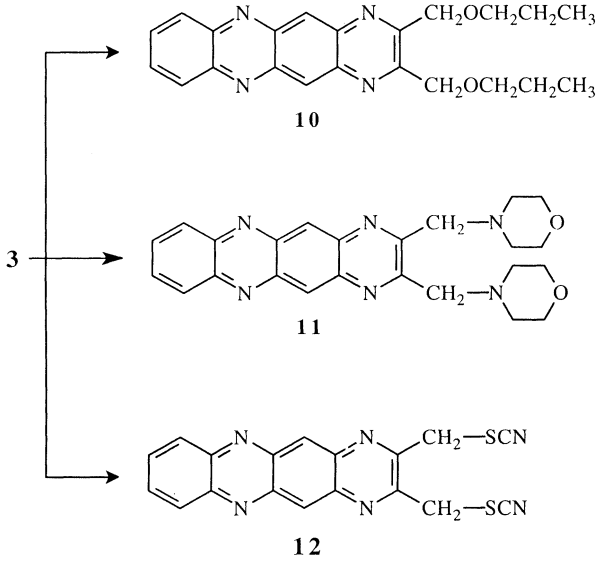


Scheme 1



Scheme 2

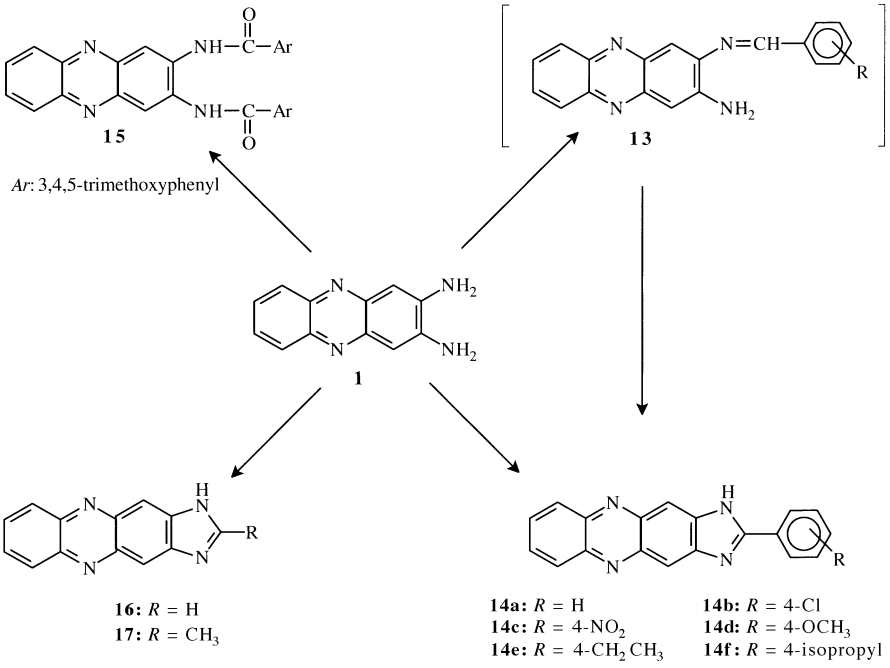
of **3** to its benzylic methylene hydrogens which are activated by the electron withdrawing effects of the pyrazine ring. Thus, the introduction of alkoxide side chains into **3** was achieved by prolonged refluxing in the corresponding alcohol. Among several alcohols tested, 1-propanol gave the cleanest product. Several by-products were removed by chromatography, and **10** was obtained in moderate yield. Continuing our efforts to substitute bromine in **3**, it was found that **3** easily reacted with morpholine and pyridine to give the dimorpholino compound **11**. The reaction of **3** with potassium thiocyanate afforded the corresponding cyanosulfanylmethyl derivative **12** (Scheme 3).



Scheme 3

Several benzimidazol derivatives exhibit remarkable bioactivity and are contained in commercially available pharmaceuticals [18, 19], *e.g.* benzimidazoles in anti-tumor agents [20], whereas others show activity against fungi [21]. Thus it was of interest to explore the scope of the above reactions by synthesizing the 1*H*-imidazo[4,5-*b*]phenazine derivatives **14a–f** from **1**. It was found that these compounds could be afforded by condensation of **1** with differently substituted aromatic aldehydes (benzaldehyde, 4-chlorobenzaldehyde, 4-nitrobenzaldehyde, 4-methoxybenzaldehyde, 4-ethyl benzaldehyde, and 5-isopropyl benzaldehyde) in nitrobenzene or dimethylformamide at reflux (Scheme 4).

This reaction proceeds *via* the initial formation of the corresponding *Schiff* bases **13a–f** which then undergo an oxidative cyclization step. The reaction



Scheme 4

conditions employed here are similar to those reported for the preparation of related 2-arylbenzimidazoles [22]: the solvent acts also as an oxidant. Our efforts to isolate the intermediate *Schiff* bases **13a–f** were unsuccessful under a variety of conditions. On the other hand, treatment of **1** with aromatic acids (4-methoxybenzoic acid, 4-ethyl benzoic acid, and 4-isopropyl benzoic acid) in the presence of $POCl_3$ under reflux [23, 24] afforded the 2-aryl-1*H*-imidazo[4,5-*b*]phenazines **14d–f** (Scheme 4). Treatment of 2,3-diaminophenazine with two mol of 3,4,5-trimethoxy benzoic acid in $POCl_3$ under reflux gave **15**. Also, **1** underwent cyclization in formic acid and/or acetic anhydride at reflux temperature to yield 1*H*-imidazo[4,5-*b*]phenazines **16** and **17**. The structure of all newly synthesized compounds was confirmed by their elemental and spectroscopic data.

Experimental

Melting points were measured on a Kofler hot stage microscope (Reichert, Vienna) and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 200 spectrometer at 200 MHz (^1H) and 50 MHz (^{13}C); chemical shifts are given in δ relative to internal *TMS* at 295 K. IR spectra are obtained on a Biorad FT-IR-45 instrument. All experiments were carried out with exclusion of moisture. For all newly synthesized compounds satisfactory elemental analyses were obtained.

Pyrazino[2,3-b]phenazine derivatives **2–7**; general procedure

A mixture of 1 mmol of 1,2-diketone and 0.21 g **1** (1 mmol) in 20 cm^3 acetic acid was heated under reflux for 5 h. The solid product obtained was filtered off and recrystallized from the given solvent to yield the corresponding condensed products **2–7**.

2,3-Dimethyl-pyrazino[2,3-b]phenazine (**2**; $C_{16}H_{12}N_4$)

Prepared from butane-2,3-dione and **1**; crystallization from *DMF* gave fine brown crystals (68%); m.p.: >350°C; IR (KBr): 3095, 1620, 1610–1480, 1450 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.85$ (s, $2CH_3$), 7.88 (m, $2H_{ar}$), 8.10 (m, $2H_{ar}$), 9.02 (s, $2H_{ar}$) ppm.

2,3-Dibromomethyl-pyrazino[2,3-b]phenazine (**3**; $C_{16}H_{10}Br_2N_2$)

Prepared from 1,4-dibromobutane-2,3-dione and **1**; crystallization from $CHCl_3$ gave faint red crystals (52%); m.p.: 225°C; IR (KBr): 3098, 2923, 1622, 1612, 1480 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 5.03$ (s, $2CH_2$), 7.90 (m, $2H_{ar}$), 8.30 (m, $2H_{ar}$), 9.15 (s, $2H_{ar}$) ppm.

2,3-Diphenyl-pyrazino[2,3-b]phenazine (**4**; $C_{26}H_{16}N_4$)

Prepared from benzil and **1**; crystallization from *DMF*/H_2O gave fine brown crystals (77%); m.p.: 220°C; IR (KBr): 3108, 1620, 1610, 1580, 1522, 1482 cm^{-1}; ^1H NMR ($CDCl_3$): 7.41 (m, $6H_{ar}$), 7.63 (m, $4H_{ar}$), 7.91 (m, $2H_{ar}$), 8.27 (m, $2H_{ar}$), 9.23 (s. $2H_{ar}$) ppm.

Phenanthraceno[1′,2′: 5,6]pyrazino[2,3-b]phenazine (**5**; $C_{26}H_{14}N_4$)

Prepared from phenanthrenequinone and **1**; crystallization from ethanol gave pink crystals (65%); m.p.: 245°C; IR (KBr): 3110, 1625, 1615, 1568, 1520, 1480 cm^{-1}; ^1H NMR ($CDCl_3$/*DMSO*-d_6): $\delta = 7.50$ (m, $3H_{ar}$), 7.62–7.84 (m, $3H_{ar}$), 8.27 (m, $5H_{ar}$), 8.55 (m, $3H_{ar}$) ppm.

Acenaphtho[1′,2′:5,6]pyrazino[2,3-b]phenazine (**6**; $C_{24}H_{12}N_4$)

Prepared from acenaphthenequinone (1 mmol) and **1**; crystallization from ethanol gave pink crystals (80%); m.p.: >350°C; IR (KBr): 3103, 3046, 1630, 1620, 1599, 1585, 1480 cm^{-1}; ^1H NMR ($CDCl_3$/*DMSO*-d_6): $\delta = 7.88$ (m, $4H_{ar}$), 8.16 (m, $4H_{ar}$), 8.42 (d, $2H_{ar}$), 9.08 (s, $2H_{ar}$) ppm.

Aceanthraceno[1′,2′: 5,6]pyrazino[2,3-b]phenazine (**7**; $C_{28}H_{14}N_4$)

Prepared from aceanthrenequinone and **1**; crystallization from *DMF* gave brown crystals (71%); m.p.: >350°C; IR (KBr): 3110, 3040, 1630, 1622, 1580, 1518, 1480 cm^{-1}; ^1H NMR ($CDCl_3$/*DMSO*-d_6): $\delta = 7.65$ (m, $2H_{ar}$), 7.81 (m, $3H_{ar}$), 8.16 (m, $4H_{ar}$), 8.45 (d, $1H_{ar}$), 8.75 (s, $1H_{ar}$), 9.08 (s, $2H_{ar}$), 9.53 (d, $1H_{ar}$) ppm.

Reaction of **2** *with N-bromo succinimide: Formation 2,3-Dibromomethyl-pyrazino[2,3-b]phenazine* (**3**; $C_{16}H_{10}Br_2N_2$)

A suspension of 0.26 g **2** (1 mmol), 0.45 g N-bromo succinimide (2.5 mmol), and 0.1 g benzene peroxide in 50 cm^3 dry benzene was refluxed with stirring for 24 h. Then, 50 cm^3 ether were added; the organic phase was washed with 50 cm^3 $NaHCO_3$ conc. and water (three times) and dried over anhydrous Na_2SO_4. After evaporation of the solvent the remaining crude product of dark red colour was recrystallized twice from acetone and $CHCl_3$ to yield 23% **3**.

Indeno[1,2-b]pyrazino[5,6-b]phenazine (**8**; $C_{21}H_{10}N_4O$)

A mixture of 0.21 g **1** (1 mmol), 0.18 g ninhydrin (1 mmol), 50 cm^3 ethanol, and 3 drops of acetic acid was refluxed for 3 h. After cooling, the formed solid was collected by suction and recrystallized from dimethyl formamide as reddish brown crystals (43%).

M.p.: 355°C; IR (KBr): 3110, 1680, 1622, 1618, 1567, 1518, 1489 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.77–7.95$ (m, $4H_{ar}$), 8.07–8.30 (m, $4H_{ar}$), 9.13 (s, $1H_{ar}$), 9.33 (s, $1H_{ar}$) ppm.

2,3-Dihydroxy-pyrazino[2,3-b]phenazine (**9**; $C_{14}H_8N_4O_2$)

A mixture of 0.21 g **1** (1 mmol), 0.21 g oxalyl chloride (1.8 mmol), and 50 cm^3 pyridine was refluxed with stirring for 5 h. After cooling, the reaction mixture was poured into 35 cm^3 H_2O and 5 cm^3 30% HCl. The precipitated product was filtered, dried, and crystallized from ethanol to give dark red crystals of **9** (38%).

M.p.: >450°C; IR (KBr): 3480 br, 1657, 1631, 1625, 1589, 1518, 1485 cm^{-1}; ^1H NMR (*DMSO*-d_6) $\delta = 7.03$ (s, $2H_{ar}$), 7.74 (m, $2H_{ar}$), 7.78 (br, 2H, 2NH), 8.02 (m, $2H_{ar}$) ppm.

2,3-Bis-(propoxymethyl)-pyrazino[2,3-b]phenazine (**10**; $C_{22}H_{24}N_4O_2$)

A solution of 0.39 g **3** (1 mmol) in 20 cm^3 1-propanol was heated under reflux for 25 h. The solvent was removed under reduced pressure. The blue solid was chromatographed on silica with CH_2Cl_2 to give a blue powder (55%).

M.p.: 140°C; IR (KBr): 3110, 3046, 2930, 1632, 1618, 1585, 1488 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 0.95$ (t, $2CH_3$), 1.66 (m, $2CH_2$), 3.47–3.88 (m, $4OCH_2$), 7.87 (m, $2H_{ar}$), 8.28 (m, $2H_{ar}$), 9.10 (d, $2H_{ar}$) ppm.

2,3-Bis-(4-morphoinylmethyl)-pyrazino[2,3-b]phenazine (**11**; $C_{26}H_{30}N_6$)

A mixture of 0.39 g **3** (1 mmol), 0.19 g morpholine (2.2 mmol), 0.17 g pyridine (2.2 mmol), and 20 cm^3 acetone was stirred at room temperature for 30 min, filtered, and the filterate was evaporated at 40°C. Water was added to the dark residue, and undissolved material was filtered off. The green solid was chromatographed on silica with $CHCl_3$/MeOH (9:1) to give a green powder (32%).

M.p.: 87–89°C; IR (KBr): 3103, 3046, 2986, 2915, 1632, 1615, 1580, 1520, 1486 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.50–2.63$ (m, 8H, $2CH_2$-N-CH_2), 3.72 (m, 8H, $2CH_2$-N-CH_2), 4.09–4.24 (m, $2CH_2$), 7.78 (m, $2H_{ar}$), 8.16 (m, $2H_{ar}$), 8.45 (s, $2H_{ar}$) ppm.

2,3-Bis-(cyanosulfanylmethyl)-pyrazino[2,3-b]phenazine (**12**; $C_{18}H_{10}N_6O_2$)

A solution of 0.20 g KSCN (2 mmol) in 5 cm^3 acetone was added dropwise to a stirred solution of 0.39 g **3** (1 mmol) in 10 cm^3 *DMF* at room temperature. The suspension was stirred for 30 min, the solvent was evaporated, and 15 ml H_2O were added to the solid residue. Water insoluble material was filtered off and washed with H_2O to yield crude **12**; recrystallization from *DMF*/H_2O this gave reddish crystals (72%).

M.p.: 233°C; IR (KBr): 3100, 3025, 2985, 2160, 1632, 1618, 1580, 1488 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 4.90$ (s, $2CH_2$), 7.79 (m, $2H_{ar}$), 8.25 (m, $2H_{ar}$). 9.15 (s, $2H_{ar}$) ppm.

Reaction of 2,3-diaminophenazine with aromatic aldehydes: Formation of 2-aryl-1H-imidazo[4,5-b]phenazine derivatives **14a–f** *(general procedure)*

To a stirred solution of 0.21 g **1** (1 mmol) in 10 cm^3 nitrobenzene or *DMF* 1 mmol of the appropriate arylaldehyde was added dropwise at room temperature. Stirring was continued for additional 30 min. The reaction mixture was refluxed for 8 h and allowed to stand overnight at room temperature. The resulting precipitate was collected, washed with ether, and recrystallized from the appropriate solvent to yield **14a–f**.

2-Phenyl-1H-imidazo[4,5-b]phenazine (**14a**; $C_{19}H_{12}N_4$)

Prepared from **1** and benzaldehyde; crystallization from *DMF* gave dark red crystals (73%); m.p.: 358–360°C as observed in Ref. [25]; IR (KBr): 3465 br, 3110, 3046, 1628, 1610, 1585, 1522, 1480 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 6.92$ (d, $2H_{ar}$), 7.56–8.32 (m, $9H_{ar}$), 13.40 (br, NH) ppm.

2-(4-Chlorophenyl)-1H-imidazo[4,5-b]phenazine (**14b**; $C_{19}H_{12}ClN_4$)

Prepared from **1** and 4-chloro-benzaldehyde; crystallization from *DMF*/H_2O gave dark brown crystals (65%); m.p.: >360°C; IR (KBr): 3469 br, 3110, 3046, 1627, 1618, 1585, 1485 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 6.92$ (d, $2H_{ar}$), 7.57 (m, $3H_{ar}$), 7.89 (m, $3H_{ar}$), 8.29 (d, $2H_{ar}$), 13.40 (br, NH) ppm.

2-(4-Nitrophenyl)-1H-imidazo[4,5-b]phenazine (**14c**; $C_{19}H_{11}N_5O_2$)

Prepared from **1** and 4-nitro-benzaldehyde; crystallization from *DMF*/H_2O gave dark brown crystals (70%); m.p.: >360°C; IR (KBr): 3460, 3100, 3046, 1630, 1610, 1585, 1522, 1486 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 6.92$ (d, $2H_{ar}$), 7.58–8.55 (m, $8H_{ar}$), 13.60 (br, NH) ppm.

2-(4-Methoxyphenyl)-1H-imidazo[4,5-b]phenazine (**14d**; $C_{20}H_{14}N_4O$)

Prepared from **1** and 4-methoxy-benzaldehyde; crystallization from ethanol gave red crystals (82%); m.p.: 360°C; IR (KBr): 3465, 3100, 3046, 2986, 1628, 1618, 1585, 1480 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 3.50$ (s, OCH_3), 7.76 (d, $1H_{ar}$), 7.93 (m, $3H_{ar}$), 8.07 (d, $1H_{ar}$), 8.29 (m, $3H_{ar}$), 9.13 (s, $1H_{ar}$), 9.33 (s, $1H_{ar}$) ppm; ^1H NMR (*DMSO*-d_6): $\delta = 3.91$ (s, OCH_3), 7.10 (d, $2H_{ar}$), 7.90 (m, $2H_{ar}$), 8.25 (m, $3H_{ar}$), 8.40–8.48 (m, $3H_{ar}$), 13.30 (br, NH) ppm; ^{13}C NMR (*DMSO*-d_6/D_2O) $\delta = 65.00$ (OCH_3), 124.50, 130.00, 135.80, 138.00, 138.95, 139.48, 151.50, 153.20, 171.50, 172.79 (aryl) ppm.

2-(4-Ethylphenyl)-1H-imidazo[4,5-b]phenazine (**14e**; $C_{21}H_{16}N_4$)

Prepared from **1** and 4-ethyl-benzaldehyde; crystallization from *DMF* gave reddish brown crystals (60%); m.p.: >360°C; IR (KBr): 3460, 3100, 3046, 2986, 2918, 1630, 1585, 1522, 1480, 1378 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.18$ (t, 3H, CH_3), 2.70 (q, 2H, CH_2), 7.19 (d, $2H_{ar}$), 7.84 (m, $3H_{ar}$), 8.19 (m, $2H_{ar}$), 8.27–8.37 (m, $3H_{ar}$) ppm.

2-(4-Isopropylphenyl)-1H-imidazo[4,5-b]phenazine (**14f**; $C_{23}H_{20}N_4$)

Prepared from **1** and 4-isopropyl-benzaldehyde; crystallization from *DMF* gave fine brown crystals (78%); m.p.: >360°C; IR (KBr): 3460 br, 3100, 3046, 2986, 1632, 1618, 1585, 1522, 1485 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.49$ (s, $2CH_3$), 2.90 (m, 1H, CH-), 7.45 (m, $5H_{ar}$), 7.77 (m, $5H_{ar}$) ppm.

Reaction of **1** *with aromatic acids: Formation of 2-aryl-1H-imidazo[4,5-b]phenazine derivatives* **14d-f** *(general procedure)*

A finely powdered mixture of 0.21 g **1** (1 mmol) and 1 mmol of the appropriate aromatic acid was added in portions to 20 cm^3 $POCl_3$ under stirring. This mixture was heated at reflux for 4 h; after cooling, the excess of $POCl_3$ was removed *in vacuo*. 100 cm^3 ice/H_2O was added to the residue, followed by aqu. NH_3 until *pH* 11. The mixture was extracted with $CHCl_3$, and the combined extracts were dried and evaporated to dryness. The crude product was recrystallized from *DMF* to give **14d–f** (20–25%).

2,3-Bis-(3,4,5-trimethoxybenzamido)-phenazine (**15**; $C_{32}H_{30}N_4O_8$)

A finely powdered mixture of 0.21 g **1** (1 mmol) and 0.42 g, 3,4,5-trimethoxybenzoic acid (2 mmol) was added in portions to 40 cm^3 $POCl_3$ with stirring. This mixture was heated at reflux for 6 h and the excess of $POCl_3$ was removed *in vacuo*. 100 ml ice/H_2O was added to the residue followed by aqu. NH_3 until *pH* 8. The precipitated product was filtered, dried, and crystallized from ethanol to give **15** (48%).

M.p.: 155°C; IR (KBr): 3350, 3078, 2974, 1686, 1628, 1558, 1507, 1490, 1458, 1433, 1389 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.88$ (s, 4OCH_3), 3.95 (s, 2OCH_3), 7.21 (s, 4H_{ar}), 7.75 (m, 2H_{ar}), 8.07 (m, 2H_{ar}), 8.42 (s, 2H_{ar}), 9.45 (br, 2NH) ppm. ^{13}C NMR ($CDCl_3$): $\delta = 65.71$ (4OCH_3), 70.55 (2OCH_3), 114.45, 137.49, 138.99, 140.00, 140.13, 143.97, 150.72, 152.83, 162.78 (aryl), 176.19 (2C=O) ppm.

1H-Imidazo[4,5-b]phenazine (**16**; $C_{13}H_8N_4$)

A suspension of 0.21 g **1** (1 mmol) in 20 cm^3 HCOOH was refluxed for 10 h in the presence of 0.50 g CH_3COONa. The greyish crystalline material which separated upon cooling was washed with 25 cm^3 H_2O, dried under reduced pressure, and recrystallized from *DMF*/H_2O to give greyish fine crystals (62%).

M.p.: 303°C; IR (KBr): 3350, 3078, 1632, 1620, 1558, 1507, 1483 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 7.87$ (m, 2H_{ar}), 8.22 (m, 2H_{ar}), 8.38 (m, 2H_{ar}), 8.50 (s, 1H_{ar}) ppm.

2-Methyl-1H-imidazo[4,5-b]phenazine (**17**; $C_{14}H_{10}N_4$)

A suspension of 0.21 g **1** (1 mmol) in 12 cm^3 acetic anhydride was heated at reflux for 30 min to give a dark yellow solution. After cooling in ice, the product was filtered off and recrystallized from acetic acid to give yellow crystals (78%).

M.p.: 320°C; IR (KBr): 3365, 3077, 2972, 1630, 1615, 1560, 1531, 1485, 1450, 1390 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.66$ (s, CH_3), 7.86 (m, 2H_{ar}), 8.20–8.33 (m, 4H_{ar}), 12.80 (br, NH) ppm.

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References

[1] Pathirana C, Jensen PR, Dwight R, Fenical W (1992) J Org Chem **57**: 740
[2] Rewcastle GR, Denny WA, Baguley BC (1987) J Med Chem **30**: 843
[3] Tipton CD, Reinhart KL (1970) J Am Chem Soc **92**: 1425
[4] Shoji J, Sakazaki R, Nakai H, Terui Y, Hatori T, Shiratori O, Kondo E, Konishi T (1988) J Antibiot **41**: 589
[5] O'Sullivan JF, Conalty ML, Morrison NE (1988) J Med Chem **31**: 567
[6] Lehn JM, Schmidt F, Vigneron JB (1988) Tetrahedron Lett **29**: 5255
[7] Gilpin LM, Fulston M, Payne DCR, Hood I (1995) J Antibiot **48**: 1081
[8] Badria AF, El-Naggar AW (1994) J Sci Pharm **62**: 355
[9] Lee HH, Palmer BD, Boyd M, Baguley BC, Denny WC (1992) J Med Chem **35**: 258
[10] Land CWW, Mocek U, Floss HG (1993) J Org Chem **58**: 6576
[11] Hazelton JC, Iddon B, Suschitzky H, Woolley LH (1995) Tetrahedron **51**: 10771

[12] Cross B, Dunn C, Payne DH, Tipton JD (1969) J Sci Food Agric **20**: 340
[13] Inone H, Noda K, Imoto E (1964) Bull Chem Soc Jpn **37**: 332
[14] Rosenberg B (1962) J Chem Phys **37**; 1371
[15] Inokuchi H (1954) Bull Chem Soc Jpn **27**: 22
[16] Kleinerman M, Azarraga L, McGlynn SP (1962) J Chem Phys **37**: 1825
[17] Rosenberg B (1958) J Chem Phys **29**: 1108
[18] Townsend LB, Wise DS (1990) Parasitology Today **6**: 107
[19] Neugebauer A (1992) J Chem Soc Perkin Trans 1, 3129
[20] Lee JC, Field DL, Lee LLY (1980) Biochemistry **19**: 6209
[21] Pereston PN (1974) Chem Rev **74**: 279
[22] El-Abadelah MM, Sabri SS, Abu-Zarga MH, Abdel-Jalil RJ (1995) Heterocycles **41** (12): 2713
[23] Middleton RW, Wibberley DG (1980) J Heterocycl Chem **17**: 1757
[24] Kutter E, Austel V (1974) Ger Patent 2, 305, 339; Chem Abstr (1975) **82**: 4215y
[25] Viktor Z, Jaroslav S, Jarslav D (1989) Czech CS 258, 596 (Cl. C07D487/04); Chem Abstr (1990) **112**: 35893b

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