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Synthesis and Antibacterial Activity of Some Substituted 3-(Aryl)- and 3-(Heteroaryl)indoles

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Summary. A synthesis of 3-(4-methoxycarbonyl-2,6-dinitrophenyl)indole, its 2,6-diamino analog, and 3-(2-amino-4-trifluoromethyl-6-nitrophenyl)indole is described. 4-(Trifluoromethyl)phenyl derivatives exhibit higher antibacterial potency than the former 4-(methoxycarbonyl)phenyl homologs, while 3-(4-trifluoromethyl-2-nitrophenyl)indole was the most active agent in the series, with MIC $\approx 7\,\mu g/cm^3$ against *E. coli* and *S. aureus.*

Keywords. 3-(Substituted)phenyl and heteroarylindoles; Antibacterial activity.

Introduction

The indole nucleus occurs naturally in a large number of secondary metabolites from plant origin (indole alkaloids), some of which serve as therapeutically useful drugs, *e.g.* harmaline, vincristine, and resperine [1]. Indole medicinal products of fungus origin include ergotamine and semi-synthetic lysergic acid diethylamide (LSD). Also, a number of naturally occurring 3-(heteroaryl)indoles were characterized and shown to possess antimicrobial activity. Examples include 3-(2-thiazolyl)indole (**1**) (called camalexine, isolated from the leaves of *Camelina sativa*/*Cruciferae* [2]), and 3-(5-oxazolyl)indoles **2a** and **2b** (called pimprinines, isolated from *Streptomyces pimprina*) [3] (Formulae 1).

In search for new lead antibacterial agents, we thought it worthwhile to test the *in vitro* antibacterial activity of model 3-(heteroaryl)indoles (**3**, **4**) and 3-(4-trifluoromethylphenyl)indoles (**5**–**8**) (Formulae 2). These compounds have previously been

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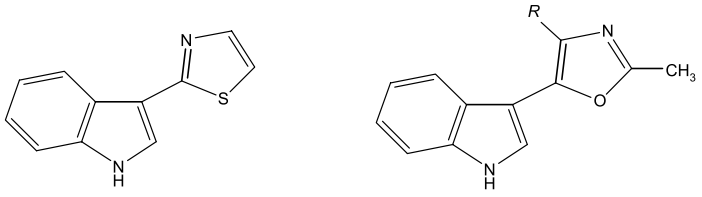
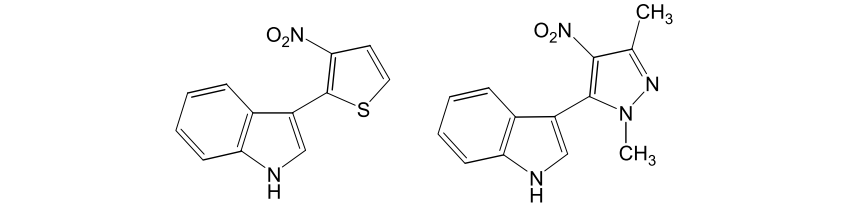
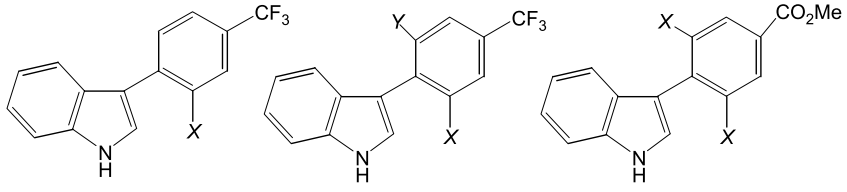


1 **2a** R = H, **2b** R = Cl

Formulae 1



3 **4**



5 $X = NO_2$
6 $X = NH_2$

7 $X = Y = NO_2$
8 $X = Y = NH_2$
9 $X = NH_2$, $Y = NO_2$

10 $X = NO_2$
11 $X = NH_2$

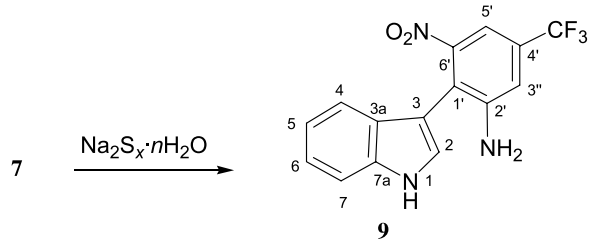
Formulae 2

utilized in the synthesis of various tetra- and pentacyclic heterocycles [4–8], and are prepared in this study for bioassay. For comparative study, **9** and 3-(4-methoxycarbonylphenyl)indoles **10** and **11** were also prepared as outlined in Schemes 1 and 2. Herein, we also report on the antibacterial data of **3–11**. The synthesis procedures and properties of the new compounds **9–11** are detailed in the experimental part.

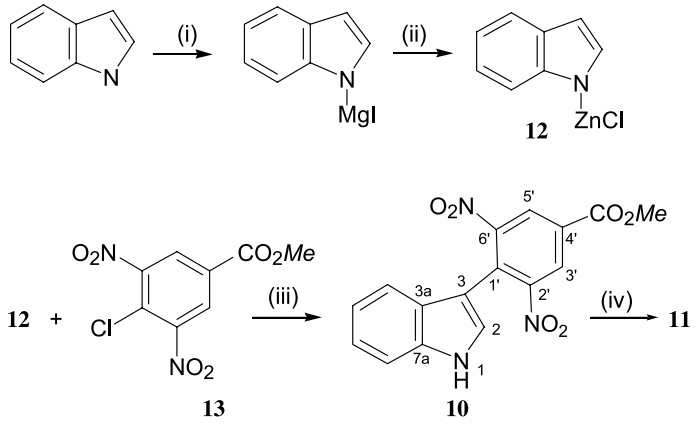
Results and Discussions

Syntheses

3-(4-Trifluoromethyl-2,6-dinitrophenyl)indole (**7**) [7] underwent reduction of one nitro group with sodium polysulfide [9] to deliver the corresponding 3-(2-amino-4-trifluoromethyl-6-nitrophenyl)indole (**9**) (Scheme 1). 3-(4-Methoxycarbonyl-2,6-dinitrophenyl)indole (**10**) has been prepared *via* coupling of indolylzinc chloride (**12**) [2, 5, 10] with methyl 4-chloro-3,5-dinitrobenzoate (**13**). The copper(II) acetate/$NaBH_4$ system [11] was employed for the re-



Scheme 1



i) *Me*MgI (3.0 *M* in Et_2O); ii) $ZnCl_2$ (1.0 *M* in Et_2O);
iii) Et_2O / 20°C; iv) $NaBH_4$, $Cu(OAc)_2$ / *Me*OH, △

Scheme 2

duction of **10** to afford 3-(2,6-diamino-4-methoxycarbonylphenyl)indole (**11**) (Scheme 2).

The IR, MS, and NMR spectral data of **7**, **10**, and **11** are in accordance with the assigned structures and are given in the experimental part. Thus, their MS spectra display the correct M^+ for which the measured HRMS data are in good agreement with the calculated values suggested by their molecular formulae. Assignments of the ^1H NMR signals to the different protons are straightforward, and ^{13}C signal assignments are based on DEPT and 2D (COSY, HMQC, HMBC) experiments, which showed correlations that helped in the assignments of the various carbons and hydrogens.

Antimicrobial Activity

In vitro antibacterial screening results of **5**–**11** showed that **5** is the most active derivative with $MIC \approx 7\,\mu g/cm^3$ against *Escherichia coli* and *Staphylococcus aureus* (representatives of *Gram*-negative and *Gram*-positive bacteria classes, *cf.* Table 1). However, these compounds showed weak to moderate antifungal activity against *Candida albicans* (ATCC 10231) and *Asperigillus niger* (ATCC 16404).

Table 1. *In vitro* antibacterial activity (*MIC* values, $\mu g/cm^3$) of different substituted 3-(trifluoromethyl)phenylindoles and of amoxycillin (**A**) and tetracycline (**T**) as reference agents

Compound	**A**	**T**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Staphylococcus aureus ATCC 6538p	1.14	1.83	7.3	14.7	14.7	14.7	>156	>156	>156
Escherichia coli ATCC 8739	2.34	1.83	7.3	29.3	29.3	58.6	29.3	58.6	117.2

Experimental

Melting points: Electrothermal melting temperature apparatus. ^1H and ^{13}C NMR spectra: Bruker DPX 300 instrument (300 MHz/75 MHz) at room temp, *TMS* as internal standard, $\delta_{TMS} = 0.00$ ppm. Electron impact mass spectra were obtained using a Finnigan MAT TSQ-70 spectrometer at 70 eV at an ion source temperature of 200°C. IR spectra (KBr) were recorded on a Nicolet Impact-400 FT-IR spectrophotometer. 1-Chloro-4-trifluoromethyl-2-nitrobenzene, 2-chloro-4-trifluoromethyl-1,3-dinitrobenzene, 4-chloro-3,5-dinitrobenzoic acid, 2-chloro-3-nitrothiophene, 5-chloro-1,3-dimethyl pyrazole, and indole were purchased from Acros, and $ZnCl_2$ (1.0 *M* in ether) and methylmagnesium iodide (3.0 *M* in ether) from Aldrich. Solvents were purified and dried according to literature procedures. Microanalyses were preformed at the Microanalytical Laboratory – Inorganic Chemistry Department, Tübingen University, Germany, and the results agreed with the calculated values within experimental errors.

3-(2-Thienyl)indole (**3**) [4], 3-(1,3-dimethyl-5-pyrazolyl)indole (**4**) [5], 3-(4-trifluoromethylphenyl)indoles (**5**, **6**) [6] and (**7**, **8**) [7] were prepared according to established procedures.

Pharmacological Tests

The minimal inhibitory concentrations (*MIC*s) were determined by the conventional broth dilution method using the two serial dilution technique. The standardization of bacterial test suspension was carried out according to *McFarland* standard method as described by the National Committee for Clinical Laboratories Standard (NCCLS, 1993). Stock solutions of the test compounds were prepared using *DMSO*. Serial dilutions were prepared to obtain test concentrations ranging from 156 $\mu g/cm^3$–0.3 $\mu g/cm^3$. Each tube was then inoculated with 0.1 cm^3 of the cultured bacteria (containing approximately 1 to 2×10^8 *CFU*/cm^3), mixed and incubated at 37°C for 24 h. Growth inhibition with concentrations at 156 $\mu g/cm^3$ or lower were carried out in duplicates. All test tubes showing positive/ negative growth were confirmed by the agar plate method. The results were recorded according to presence and absence of growth. The *MIC*s were calculated as the average concentration of the test agent in the broth tubes showing consecutive positive and negative growth.

Methyl 4-chloro-3,5-dinitrobenzoate (**13**)

Thionyl chloride (10 cm^3) was added dropwise to a stirred and cooled (0°C) solution of 4.9 g 4-chloro-3,5-dinitrobenzoic acid (20 mmol) in absolute *Me*OH (100 cm^3). The resulting mixture was then heated at reflux for 2 h. Thereafter, the solvent was distilled off, and the residual solid product was recrystallized from petrolum ether (bp 60–80°C). Yield 4.6 g (88%); mp 105–106°C (Ref. [12] 102–103°C); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.03$ (s, CO_2CH_3), 8.61 (s, H-2 + H-6) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 53.6$ (OCH_3), 124.8 (C-4), 128.2 (C-2 + C-6), 130.9 (C-1), 149.7 (C-3 + C-5), 162.4 (C=O) ppm.

3-(4-Methoxycarbonyl-2,6-dinitrophenyl)indole (**10**, $C_{16}H_{11}N_3O_6$)

A solution of 8 cm^3 CH_3MgI in ether (3.0 *M*) was added to a solution of 2.3 g indole (20 mmol) in 40 cm^3 anhydrous ether and stirred at room temp for 20 min. To this mixture 24 cm^3 of a solution

of anhydrous $ZnCl_2$ in dry ether (1.0 *M*) were added and stirred at room temp for 30 min. Thereafter, 2.6 g **13** (10 mmol) were added to the reaction mixture, which was further stirred at room temp for 4 h. The resulting mixture was then treated with 100 cm^3 H_2O and stirred for 15 min. The ether layer was separated and the aqueous layer was extracted with ether (3×50 cm^3). The combined ethereal portions were dried (Na_2SO_4), and the solvent was evaporated. The residual solid product was collected and recrystallized from $CHCl_3$/petroleum ether (bp 60–80°C) to afford **10** as yellow solid. Yield 1.6 g, (47%); mp 196–197°C; MS-EI: m/z (%) = 341 (M^+, 100), 310 (8), 295 (16), 266 (7), 235 (12), 206 (18), 179 (20), 151 (13), 119 (9), 95 (23); HRMS: calcd for M^+ 341.0647, found 341.06554; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.04 (s, CH_3), 7.16 (dd, J = 7.0, 7.5 Hz, H-5), 7.23 (d, J = 7.0 Hz, H-4), 7.27 (dd, J = 7.5, 8.2 Hz, H-6), 7.40 (d, J = 2.8 Hz, H-2), 7.42 (d, J = 8.2 Hz, H-7), 8.54 (br s, N-H), 8.59 (s, H-3′ + H-5′) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.4 (O*C*H$_3$), 104.9 (C-3), 111.9 (C-7), 118.1 (C-4), 121.5 (C-5), 123.6 (C-6), 124.8 (C-2), 125.8 (C-3a), 127.0 (C-3′ + C-5′), 127.5 (C-1′), 130.7 (C-4′), 151.8 (C-2′ + C-6′), 163.2 (C=O) ppm.

3-(2,6-Diamino-4-methoxycarbonylphenyl)indole (**11**, $C_{16}H_{15}N_3O_2$)

Sodium borohydride (1.9 g, 40 mmol) was added portionwise to a stirred solution of 1.65 g **10** (5 mmol) in 60 cm^3 *Me*OH at room temp and mixed with 20 cm^3 of a saturated aqueous solution of copper acetate, whereby the reduction was completed within 4–6 h. The resulting mixture was then treated with 100 cm^3 ether and washed with 10% aqueous Na_2CO_3 solution. The ether layer was separated, and the aqueous layer was extracted with diethyl ether (2×40 cm^3). The combined ether fractions were dried (Na_2SO_4), and the solvent was then removed. The residual solid product was collected and recrystallized from CH_2Cl_2/petroleum ether (bp 40–60°C) to afford bright red needles. Yield 1.1 g (76%); mp 192–193°C; MS-EI: m/z (%) = 281(M^+, 100), 250 (7), 222 (14), 205 (7), 193 (3), 166 (13), 149 (10), 125 (8), 111 (28), 97 (18); HRMS: calcd for M^+ 281.116405, found 281.118015; ^{1}H NMR (300 MHz, *DMSO*-d_6): δ = 3.79 (s, O*CH*$_3$), 4.49 (br s, 2NH_2), 6.69 (s, H-3′ + H-5′), 6.98 (dd, J = 7.3, 7.7 Hz, H-5), 7.13 (dd, J = 7.3, 7.8 Hz, H-6), 7.17 (d, J = 7.7 Hz, H-4), 7.37 (br d, J = 2.0 Hz, H-2), 7.45 (d, J = 7.8 Hz, H-7), 11.37 (br s, N–H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): δ = 52.1 (OCH_3), 104.4 (C-3′/C-5′), 107.9 (C-3), 109.4 (C-1′), 112.3 (C-7), 119.3 (C-4), 119.8 (C-5), 121.9 (C-6), 125.5 (C-2), 126.1 (C-3a), 129.4 (C-4′), 137.2 (C-7a), 147.9 (C-2′/C-6′), 167.7 (C=O) ppm.

3-(2-Amino-4-trifluoromethyl-6-nitrophenyl)indole (**9**, $C_{15}H_{10}F_3N_3O_2$)

An aqueous solution of sodium polysulfide was freshly prepared according to Ref. [9]: A solution of 2.7 g crystalline $Na_2S{\cdot}9H_2O$ (11 mmol) in 10 cm^3 H_2O was treated with 0.65 g finely powdered S_8 (20 mmol) and warmed until a clear solution was produced. A stirred mixture of 3.5 g **7** [7] (10 mmol), 15 cm^3 H_2O, and 10 cm^3 *Et*OH was brought to gentle boiling in a beaker. To this solution was dropwise added the freshly prepared aqueous solution of $Na_2S_x{\cdot}nH_2O$, and the resulting reaction mixture was vigorously stirred and boiled for further 20 min. The resultant mixture was cooled, filtered, and the filtrate was acidified with 13 cm^3 20% aqueous HCl and boiled for 15 min. The reaction mixture was filtered, cooled, and basified with an excess of 25% aqueous NH_3. The precipitated solid was collected and recrystallized from aqueous *Et*OH in the form of fine orange needles. Yield 2.3 g (72%); mp 243–245°C; MS-EI: m/z (%) = 321 (M^+, 100), 304 (23), 302 (6), 275 (49), 274 (56), 247 (25), 226 (5), 206 (18), 178 (5), 152 (7), 137 (11), 127 (7), 113 (6), 103 (7); HRMS: calcd for M^+ 321.072479, found 321.075226; ^{1}H NMR (300 MHz, *DMSO*-d_6): δ = 4.33 (br s, NH_2); 6.59 (dd, J = 7.6, 7.8 Hz, H-5), 6.66 (d, J = 7.8 Hz, H-4), 7.02 (m, H-6 + H-7), 7.92 (br d, J = 2.0 Hz, H-2), 8.01 (br s, H-3′), 8.18 (br s, H-5′), 12.51 (br s, N_1–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 112.9 (q, $^3J_{C\text{-}F}$ = 3.7 Hz, C-3′), 114.0 (C-3), 114.7 (C-7), 114.8 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, C-5′), 116.3 (C-4), 119.8 (C-1′), 120.5 (C-3a), 120.7 (q, $^2J_{C\text{-}F}$ = 34 Hz, C-4′), 124.8 (q, $^1J_{C\text{-}F}$ = 254 Hz, *C*F$_3$), 128.0 (C-5), 129.9 (C-6), 133.7 (C-2), 136.8 (C-7a), 143.1 (C-2′), 147.4 (C-6′) ppm.

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