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The synthesis of 2- and 3-aryl indoles and 1,3,4,5-tetrahydropyrano[4,3-*b*]indoles and their antibacterial and antifungal activity

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ABSTRACT

A series of 2- and 3-aryl substituted indoles and two 1,3,4,5-tetrahydropyrano[4,3-*b*]indoles were synthesized from indole and 5-methoxyindole. The 2-aryl indoles were synthesized from the 1-(phenylsulfonyl)indole derivatives using magnesiation followed by iodination. The 2-iodinated compounds were then subjected to Suzuki–Miyaura reactions. In addition, the 3-aryl indoles were made from the corresponding 3-bromoindoles using Suzuki–Miyaura reactions. The 1,3,4,5-tetrahydropyrano[4,3-*b*]indoles were also synthesized from 1-(phenylsulfonyl)indole by magnesiation followed by treatment with allylbromide. The product was then converted into [2-allyl-1-(phenylsulfonyl)-1*H*-indol-3-yl]methanol which upon exposure to $Hg(OAc)_2$ and $NaBH_4$ afforded tetrahydropyrano[4,3-*b*]indoles. A number of the 2- and 3-aryl indoles displayed noteworthy antimicrobial activity, with compound **13a** displaying the most significant activity (3.9 μg/mL) against the Gram-positive micro-organism *Bacillus cereus*.

Indole and its derivatives play an important role as biologically active compounds.[1] As part of our research programme of particular interest to us is their role in combating bacterial and fungal infections. For example, 5-nitro-2-phenylindole (INF55, **1**) is a promising lead in helping a wide range of antibiotics stay in bacterial cells (Fig. 1).[2] This is because efflux pumps in particularly, Gram-positive bacteria are capable of extruding a wide range of antibiotics.

Other 2-aryl substituted indoles such as **2** have been implicated in inhibition of bacterial histidine kinases.[3] Another example of an active compound of this class would be 3-phenylindole **3** which is an inhibitor of brassinin glucosyltransferase, a phytoalexin detoxifying enzyme from the fungus, *Sclerotinia sclerotiorum*.[4]

Indoles containing a fused pyran at the 2- and 3-positions such as (*S*)-etodolac **4** (Fig. 2), are also of importance, but not necessarily for research related to the discovery of antibacterial and fungal agents. For example, (*S*)-**4** is a clinically effective anti-inflammatory agent and has the potential to retard the progression of skeletal changes in rheumatoid arthritis.[5,6] Other examples would include (*R*)-**5** which is a selective hepatitis C virus NS5B polymerase inhibitor.[7]

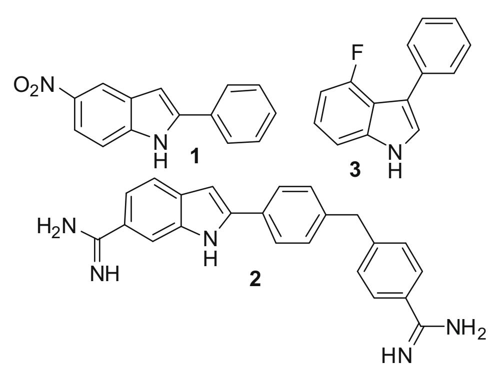

Figure 1.

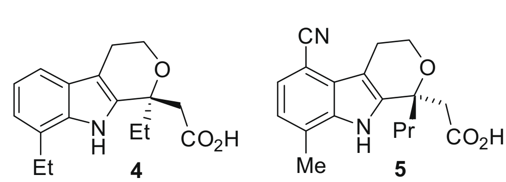

Figure 2.

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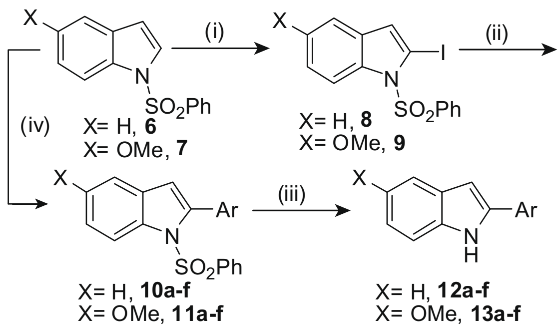


Scheme 1. Reagents and conditions: (i) (a) *i*PrMgCl, (*i*Pr)$_2$NH, THF, I$_2$, X = H, 79%, X = OMe, 89%; (ii) 10% Pd(PPh$_3$)$_4$, DME/EtOH, aq Na$_2$CO$_3$, Aryl boronic acid **14a**–**e** (Fig. 3), reflux, for yields see Table 1; (iii) K$_2$CO$_3$, MeOH, for yields see Table 1; (iv) (a) *i*PrMgCl, (*i*Pr)$_2$NH, THF; (b) 5% Pd(PPh$_3$)$_4$, 2 equiv 1,4-dibromo-2,5-dimethoxybenzene **14f** for the preparation of **10f** and **11f**.

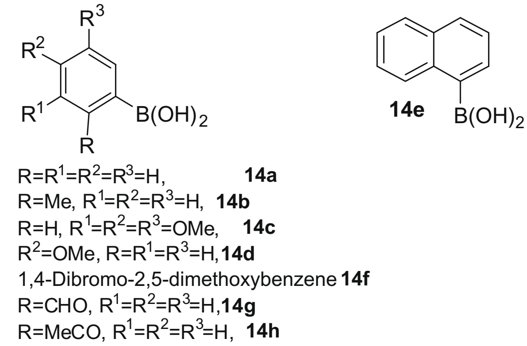


Figure 3.

Therefore the synthesis of 2- and 3-substituted indoles and their pyran fused analogues are important targets for organic synthesis. These compounds can then be tested as potential bacterial and fungal inhibitors.

In this Letter the synthesis of a series of 2- and 3-aryl substituted indoles and their testing against bacterial and yeast cell lines are reported. The synthesis of two pyran fused indoles by using related synthetic methods is also disclosed.

The magnesiation of indoles was reported in 1996 by Kondo and Sakamoto[8] as a useful method for adding substituents onto the 2-position of the indole nucleus. More recently in the group of Dinsmore, the magnesiation has been extended to *N*-phenylsulfonylpyrroles and made catalytic.[9] As a result it was decided to take advantage of this development to make a series of 2-aryl substituted indoles.

Treatment of both 1-(phenylsulfonyl)indole **6** and the methoxyindole derivative **7** with the catalytic magnesiation conditions developed by Dinsmore, followed by reaction with iodine resulted in the formation of the two iodinated precursors **8** and **9**. These compounds, containing an iodine atom in the 2 position of the indole nucleus, proved to be suitable for palladium-catalysed Suzuki–Miyaura reactions (Scheme 1). As shown in Table 1, exposure of **8** to a range of aromatic boronic acids **14a**–**e** (for structures see Fig. 3) in the presence of palladium catalyst Pd(PPh$_3$)$_4$ afforded the required 2-aryl substituted indoles **10a**–**e** in mediocre to good yields (44–82%).[10] In a similar manner, treatment of **9** with boronic acids **14a**–**e** gave **11a**–**e** in fair to good yield (60–78%). Exposure of each of these substrates **10a**–**e** and **11a**–**e** to potassium carbonate in methanol resulted in the formation of the desired 2-aryl substituted indoles **12a**–**e** and **13a**–**e** that could be tested against a range of bacterial and fungal cell lines. In addition, as shown in Scheme 1, utilising the Dinsmore magnesiation conditions on compound **6** and **7**, followed by the addition of 1,4-dibromo-2,5-dimethoxybenzene resulted in the direct formation of **10f** and **11f** without proceeding via the corresponding indole iodides **8** or **9**. Subsequently, both **10f** and **11f** were also efficiently converted into **12f** and **13f** in yields of 52% and 40%, respectively.

To place a halogen in the 3-position of the indole nucleus, compound **6** was treated with bromine in acetic acid to yield **15** (Scheme 2). In addition, indole **7** was subjected to NBS and benzoyl peroxide in CCl$_4$ to afford **16**. Both **15** and **16** were then subjected to Suzuki–Miyaura reactions with the boronic acids **14a**–**d** used previously, as well as the carbonyl containing boronic acids **14g** and **14h** (Fig. 3), to afford 14 3-aryl substituted indoles **17** and **18** in good yields. All of these products were subsequently treated with potassium carbonate in methanol to remove the phenylsulfone group resulting in the formation of the desired 3-aryl substituted indoles **19** and **20** (64–94%).

It was then desired to extend the methodology to the synthesis of 1,3,4,5-tetrahydropyrano[4,3-*b*]indoles[11] in a series of simple related steps. Starting from the same protected indole as used earlier in the work, compound **6** was reacted under the magnesiation conditions used previously, followed by quenching with allyl bromide to afford **21** in a mediocre yield (Scheme 3). Subjecting **21** to Cl$_2$CHOCH$_3$ and TiCl$_4$ at low temperature then gave **22** in good

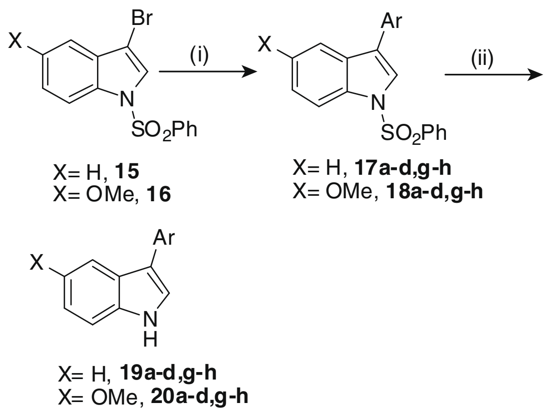
Table 1
Yields of compounds formed in Scheme 1

Entry	Ar	C$_6$H$_5$	2-MeC$_6$H$_4$	3,4,5-(MeO)$_3$C$_6$H$_2$	4-MeOC$_6$H$_4$	1-Naphthyl	2,5-(MeO)$_2$-4-BrC$_6$H$_2$
1	X = H, **10**	**10a**, 82%	**10b**, 44%	**10c**, 56%	**10d**, 60%	**10e**, 60%	**10f**, 21%
2	X = OMe, **11**	**11a**, 60%	**11b**, 78%	**11c**, 77%	**11d**, 61%	**11e**,[a]	**11f**, 35%
3	X = H, **12**	**12a**, 78%	**12b**, 82%	**12c**, 51%	**12d**, 52%	**12e**, 52%	**12f**, 52%
4	X = OMe, **13**	**13a**, 61%	**13b**, 67%	**13c**, 86%	**13d**, 51%	**13e**,[a]	**13f**, 40%

[a] Reaction not performed.

Table 2
Yields of compounds formed in Scheme 2

Entry	Ar	C$_6$H$_5$	2-MeC$_6$H$_4$	3,4,5-(MeO)$_3$C$_6$H$_2$	4-MeOC$_6$H$_4$	2-(CHO)C$_6$H$_4$	2-(CH$_3$CO)C$_6$H$_4$
1	X = H, **17**	**17a**, 89%	**17b**, 68%	**17c**, 83%	**17d**, 82%	**17g**, 67%	**17h**, 84%
2	X = OMe, **18**	**18a**, 86%	**18b**, 95%	**18c**, 60%	**18d**, 83%	**18g**, 76%	**18h**, 77%
3	X = H, **19**	**19a**, 81%	**19b**, 64%	**19c**, 65%	**19d**, 79%	**19g**, 72%	**19h**, 92%
4	X = OMe, **20**	**20a**, 85%	**20b**, 86%	**20c**, 72%	**20d**, 72%	**20g**, 94%	**20h**, 82%

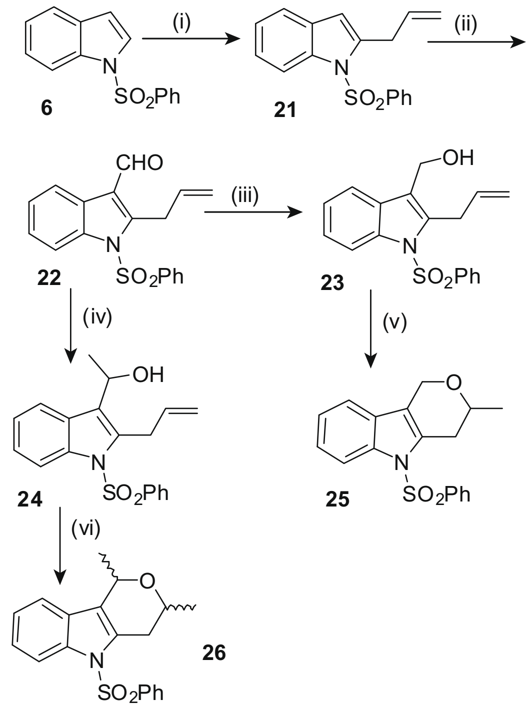


Scheme 2. Reagents and conditions: (i) 10% $Pd(PPh_3)_4$, DME/EtOH, aq Na_2CO_3, aryl boronic acid **14a**–**d**, **g**–**h** (Fig. 3), reflux, for yields see Table 2; (ii) K_2CO_3, MeOH, for yields see Table 2.

yield. This product **22** was subsequently reduced with $NaBH_4$ to yield primary alcohol **23**. Alternatively, the aldehyde **22** was exposed to MeMgBr to afford the secondary alcohol **24**. Both alcohol **23** and **24** were separately treated with $Hg(OAc)_2$, followed by reduction with $NaBH_4$ to furnish the desired pyran fused indoles **25** and **26**. As expected, pyran **26** was produced as a mixture of cis- and trans-diastereoisomers.[12]

Antimicrobial and antifungal testing: A range of the 2-and 3-substituted indoles of general structure **12**, **13**, **19** and **20** were quantitatively evaluated for antimicrobial activity using the minimum inhibitory concentration (MIC) assay.[13] These compounds were tested against a number of reference test organisms including Gram-positive (*Staphylococcus aureus* ATCC 6538 and *Bacillus cereus* ATCC 11778), Gram-negative (*Escherichia coli* ATCC 8739 and *Klebsiella pneumoniae* ATCC 8739) and yeasts (*Candida albicans* ATCC 10231 and *Cryptococcus neoformans* ATCC 90112).[14]

The in vitro antimicrobial MIC screening results for compounds **12, 13, 19** and **20** are given in Table 3. Compounds with antimicrobial activities of 64–100 μg/mL were accepted as having clinical relevance[15] and compounds with activities 10 μg/mL or less were considered significant.[16] All compounds indicating notable antimicrobial activity are indicated in bold (Table 3).



Scheme 3. Reagents and conditions: (i) *i*PrMgCl, (*i*Pr)$_2$NH, THF, CH_2=$CHCH_2Br$, 31%; (ii) Cl_2CHOMe, $TiCl_4$, CH_2Cl_2, −78 °C, 81%; (iii) $NaBH_4$, EtOH, 71%; (iv) MeMgBr, Et_2O, 76%; (v) (i) $Hg(OAc)_2$, THF, (ii) $NaBH_4$, aq NaOH, 31% (vi) (i) $Hg(OAc)_2$, THF; (ii) $NaBH_4$, aq NaOH, 25%.

The highest activities noted against both Gram-positive pathogens (*S. aureus* and *B. cereus*) were shown by compounds **19a**, **20a** and **20b**. Selective antimicrobial activity against *B. cereus* was only observed for compounds **12c**, **13a** and **20g** having MIC values of 3.9, 78 and 20 μg/mL, respectively. These compounds are all structurally similar. The most significant antimicrobial activity noted, was for compound **13a** having an MIC value of 3.9 μg/mL against *B. cereus* (see Fig. 4).

Table 3
Antimicrobial and antifungal activity of selected indole compounds

Compound	Pathogen (MIC μg/mL)					
	Staphylococcus aureus **ATCC 6538**	*Bacillus cereus* **ATCC 11778**	*Escherichia coli* **ATCC 8739**	*Klebsiella pneumoniae* **ATCC 13831**	*Candida albicans* **ATCC 10231**	*Cryptococcus neoformans* **ATCC 90112**
12a	469	625	1250	313	156	625
12c	469	**20**	313	391	117	313
12d	635	156	625	313	156	**58.5**
12e	625	625	938	313	156	625
13a	156	**3.9**	*	469	469	*
13b	235	156	468	313	313	ND
13c	313	156	625	313	156	**32.5**
13d	625	313	*	313	235	ND
19a	**39.0**	**19.5**	156	469	**19.5**	**65.1**
19c	*	235	313	313	313	**29.3**
19d	469	625	*	208	156	**78**
19f	156	235	469	313	156	261
20a	**39.1**	**15.6**	625	313	**78**	235
20b	**29.3**	**19.5**	313	313	117	625
20c	313	156	313	313	313	**29.3**
20d	313	156	521	261	156	**29.3**
20g	156	**78**	235	313	156	313
20h	625	156	313	313	235	39
Control[17]	0.3	0.08	0.08	0.8	2.5	2.5

ND = Not determined due to insufficient sample.
* = Not active at highest concentration tested (1250 μg/mL).

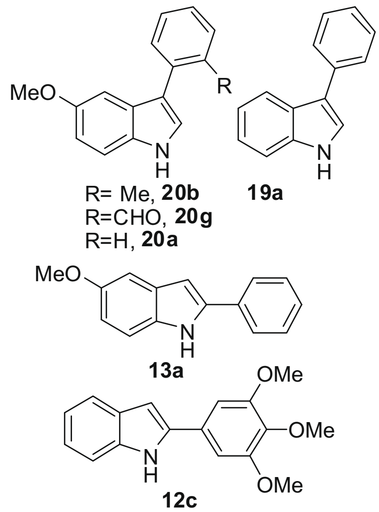


Figure 4.

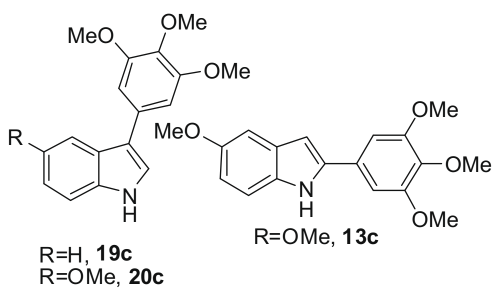


Figure 5.

All compounds were poorly active against the Gram-negative pathogens. This has been noted previously for other indole derivatives.[18]

For the yeasts, in general the compounds tested were more active against *C. neoformans.* For example, compounds **13c**, **19c** and **20c** all containing a number of methoxy substituents (Fig. 5) showed similar antifungal activity against *C. neoformans* with MIC values of 29.3, 32.5 and 29.3 μg/mL, respectively.

Acknowledgments

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14. Compounds at a starting concentration of 5 mg/mL, dissolved in acetone, were introduced (100 μL) into the first well of a microtitre plate containing 100 μL sterile water. Serial doubling dilutions were then performed so that concentrations of the compound were reduced by half with each dilution. A fixed concentration of microbial culture (100 μL) yielding an inoculum size of 1×10^6 colony forming units/mL was added to all wells and incubated at 37 °C for 24 h. The yeasts were incubated for a further 24 h. A 0.2 mg/mL *p*-iodonitrotetrazolium violet (INT) solution was prepared and 40 μL transferred to all inoculated wells. The plates were examined after 6 h or 24 h for either bacteria or yeasts, respectively to determine a colour change in relation to concentration of microbial growth .The MIC was calculated as the lowest concentration having no evidence of microbial growth. Negative controls (acetone solvent) were included to confirm that the diluents had no effect on the antimicrobial activity. Positive controls (ciprofloxacin for bacteria and amphotericin B for yeasts at starting concentrations of 0.01 mg/mL) were included to confirm susceptibility of test organisms. Assays were repeated at least in triplicate on consecutive days.
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