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Analogues of 4,5-bis(3,5-Dichlorophenyl)-2-Trifluoromethyl-1*H*-Imidazole as Potential Antibacterial Agents.

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Abstract: A preliminary exploration of analogues of 4,5-bis(3,5-dichlorophenyl)-2-trifluoromethyl-1*H*-imidazole, **1**, as novel antibacterial agents was carried out to determine the basic features of the structure responsible for the observed biological activity. The presence of two aryl rings, the imidazole NH and either a good electron withdrawing group or an aldehyde or amino group at C-2 were required for good levels of activity against methicillin resistant *Staphylococcus aureus* (MRSA).

Introduction.

The resistance of common pathogens to standard antibiotic therapies is rapidly becoming a major public health problem throughout the world. The incidence of multidrug-resistant Gram-positive bacteria is increasing, and infections caused by *S. aureus* (MRSA and coagulase-negative *Staphylococcus*), enterococci and pneumococci are particularly problematic.[1] There is a real perceived need for the discovery of new compounds endowed with antibacterial activity, possibly acting through mechanisms of action which are distinct from those of the well-known classes of antibacterial agents to which many clinically relevant pathogens are now resistant.

The 4,5-diphenylimidazoles were identified as a class of potential candidates for optimisation as focused spectrum antibiotics during a high throughput screening campaign designed to detect compounds with activity at the level of bacterial cell-wall biosynthesis. Compounds belonging to this class were subsequently found to be inactive in a transglycosylase assay and to exhibit whole cell activity against selected Gram positive organisms while they were inactive against *Acholeplasma laidlawii* and *Saccharomyces cerevisiae.* This information supports a mechanism of action exerted at the level of the cell-wall although the details of the mode of action remain obscure. The most potent example of a series of 4,5-diphenylimidazoles bearing lipophilic electron withdrawing groups on the aryl rings and an electron withdrawing trifluoromethyl group in the 2-position is shown in Figure 1.

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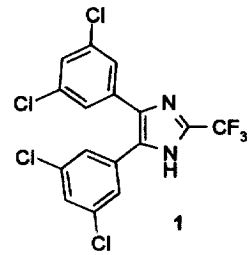


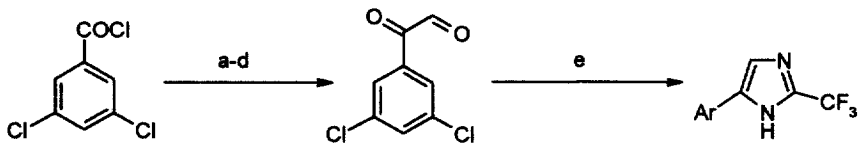
1

Figure 1

Chemistry

In order to confirm the necessity of having two aryl rings, the synthesis of the monoaryl analogue of **1** was carried out as shown in Scheme 1. The required ketoaldehyde **3** was synthesised *via* the oxidation of the bromoketone with dimethylsulfoxide.

Scheme 1

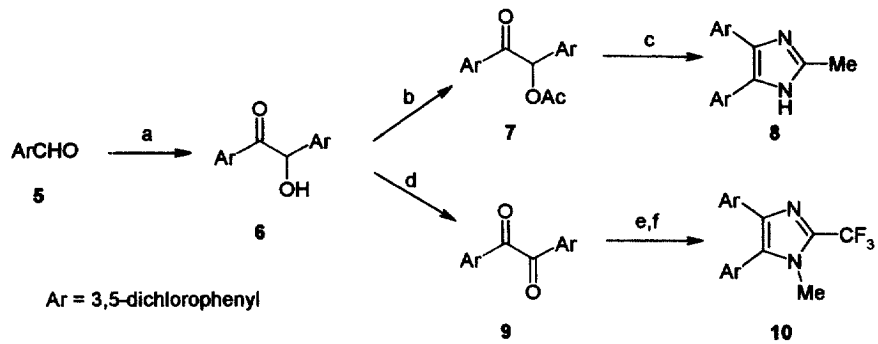


2 **3** **4**

reagents: a) Trimethylsilyldiazomethane (see ref. 2); b) HBr / AcOH; c) DMSO (see ref. 3); d) water; e) $CF_3CH(OEt)OH$ / AcOH / NH_4OAc / 110°C

The 2-methyl analogue **8** was prepared to investigate the effect of having the strongly electron withdrawing trifluoromethyl group in position 2 of the imidazole ring. The target molecule was synthesised from the acetyl derivative of the benzoin by fusion with ammonium acetate following a literature procedure.[4] The *N*-methyl derivative of **1** was prepared *via* reaction of the anion with methyl triflate in DMF at 0°C to test the hypothesis that the imidazole NH was a necessary requirement for biological activity.

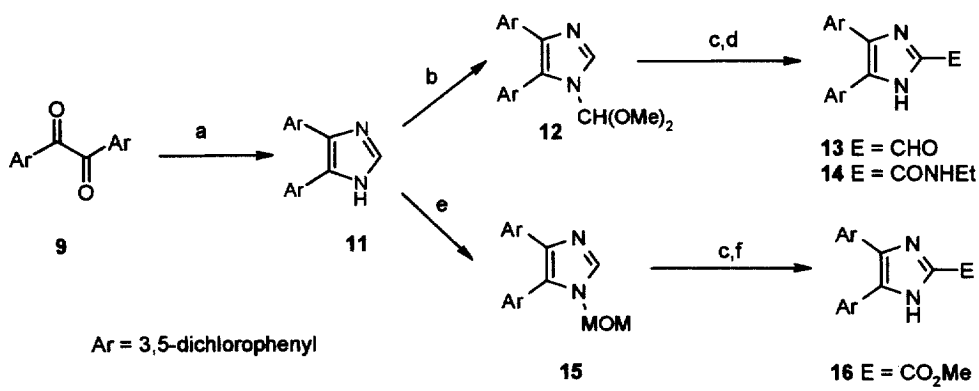
Scheme 2



reagents: a) 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide / DMF; b) AcCl / pyridine; c) NH_4OAc / 140°C; d) $CuSO_4$ / pyridine (see ref. 5); e) $CF_3CH(OEt)OH$ / AcOH / NH_4OAc / 110°C; f) NaH / DMF then MeOTf

The replacement of the trifluoromethyl group with a carbonyl group was explored through directed metallation chemistry at C-2 as shown in Scheme 3.[6] The aldehyde **13** and the ethyl carboxamide **14** were prepared *via* metallation of the orthoformate **12** followed by quenching with DMF or ethyl isocyanate, respectively. In general, the yields were very poor using **12** and therefore the more stable and easier to handle MOM group was introduced to allow the use of this reaction for the preparation of other derivatives such as the ester **16**.

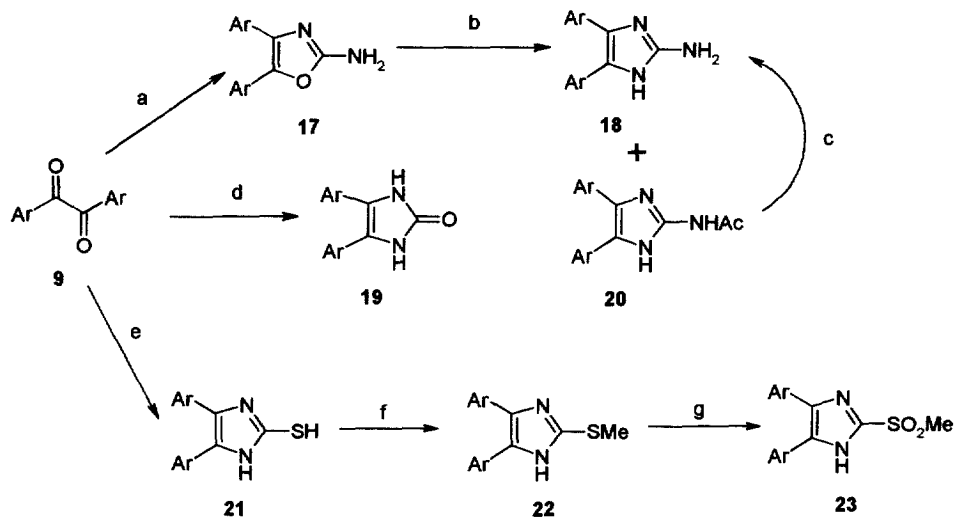
Scheme 3



reagents: a) $(CH_2O)_n$ / AcOH / NH_4OAc / 110°C; b) $CH(OMe)_3$ / reflux; c) ^nBuLi / THF / -40°C then E+ at -78°C; d) HCl aq; e) NaH / DMF / MOMCl; f) HCl in dichloromethane, r.t. 3h;

Analogues of **1** in which the trifluoromethyl group was replaced by a heteroatom were prepared from the diketone **9** according to Scheme 4. Compound **9** reacted with cyanamide in refluxing ethanol to give the 4,5-diaryl-2-amino-oxazole **17** in a yield of 27%.[7] An attempt to prepare **17** *via* the reaction of urea with **9** in the presence of sodium ethoxide as base gave the imidazolone **19** as the only product. The amino-oxazole was readily converted into the 2-aminoimidazole derivative **18** by heating at 140°C with ammonium acetate.[8] The *N*-acetyl derivative **20** was also formed during this reaction, however, this was easily hydrolysed to the desired compound using hydrochloric acid in methanol. The diketone **9** reacted readily with thiourea to give the thione **21** which was alkylated with methyl iodide to give the 2-methylthio derivative **22**.[9] The methyl sulfone was prepared by *m*CPBA oxidation of the thiomethyl compound.

Scheme 4



Ar = 3,5-dichlorophenyl

reagents: a) NH_2CN / EtOH / reflux; b) NH_4OAc / 140°C; c) HCl aq / MeOH; d) urea / EtONa / EtOH / reflux; e) thiourea / DMF / 140°C; f) NaH / MeI / THF / 45°C; g) *m*CPBA / CH_2Cl_2

Results and Discussion

The derivatives prepared were tested against a representative panel of micro-organisms and the results are collected in Table 1 along with data from compound **1** for comparison. It can be seen that some of these compounds exhibit good levels of activity against Gram positive bacteria, including *S. aureus*.

Table 1: Antibacterial Activities of Analogues of 1

Entry	*compound*	*MRSA*	*B.s.*	*E.c. pm*	*E.c.+*
1	**1**	0.25	4	>32	16
2	**4**	16	16	>32	8
3	**8**	>32	>32	>32	>32
4	**10**	8	4	>32	>32
5	**13**	2	2	>32	>32
6	**14**	>32	>32	>32	>32
7	**16**	>32	>32	>32	>32
8	**18**	2	4	>32	2
9	**11**	>32	4	>32	8
10	**21**	>32	>32	>32	>32
11	**22**	>32	>32	>32	>32
12	**23**	4	4	>32	4
13	**19**	8	4	>32	8

note: MRSA = Methicillin Resistant *Staphylococcus aureus*; B.s. = *Bacillus subtilis*; E.c. = *Escherichia coli* (permeable mutant); E.c.+ = *Escherichia coli* permeable mutant + polymixin. Minimum Inhibitory Concentrations (MIC) determined in Mueller-Hinton broth with an inoculum = 5×10^5 $CFUml^{-1}$ according to standard procedures and given as $\mu g ml^{-1}$.[10]

The preparation of the analogues of **1** described above allowed us to define some of the requirements for antibacterial activity present in the parent structure. The replacement of the strongly electron withdrawing trifluoromethyl group by a relatively poor EWG leads to a complete loss of activity, except in the case of the aldehyde **13**. The amine **18** also maintained good levels of activity despite the fact that it is not electron withdrawing in this system. The antibacterial activities of some aminoimidazole derivatives have been previously reported in the literature.[11] The sulfone **23** also represents a reasonable substitution for the trifluoromethyl group. However, none of these compounds exhibit activities at the same level as the parent. While blocking the imidazole NH through methylation also led to a fall in activity, the effect was not very marked. The lack of activity against the Gram negative organism *E.coli* is probably due to lack of permeability. This is supported by gains in activity for some of the compounds when tested against the same

strain in the presence of the permeabilizer polymixin. The lower activity of the monoaryl derivative illustrates the relative importance of having two aryl rings.

The reasonable levels of activity observed for some of these compounds against *MRSA* has prompted further investigations of the class which will be reported in due course.

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