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Novel sulfamoylbenzoates as antifungal agents against *Malassezia furfur*

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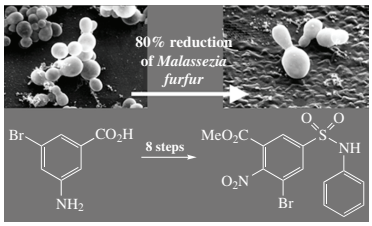
Novel polyfunctional arenesulfonamides as potential fungicides were prepared in eight steps from 3-amino-5-bromobenzoic acid. Among them, methyl 3-bromo-2-nitro-5-(*N*-phenylsulfamoyl)benzoate exhibiting significant cytotoxic activity against *Malassezia furfur* is proposed as a lead for the development of drug candidates against skin diseases caused by the fungi, especially against seborrheic dermatitis.



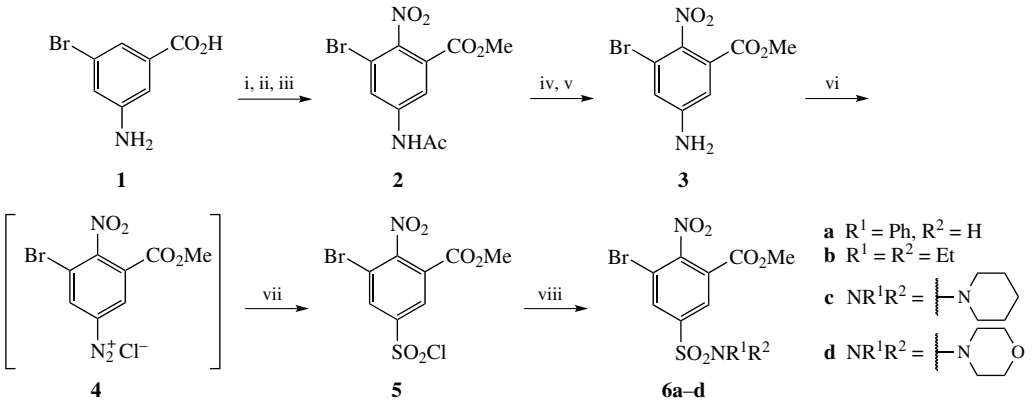
Keywords: fungicides, medicinal chemistry, arenesulfonamides, *Malassezia furfur*, seborrheic dermatitis.

Among its many functions, the skin acts as a vital barrier against pathogens.[1–3] Residential microbiomes, including the lipophilic species of *Malassezia*, are normally found on the skin surface.[4,5] However, under certain conditions, such as immune deficiency, diseases that hamper the skin barrier as well as wounds, these species might be transformed to opportunistic pathogens that might be involved in diverse dermatological disorders and even systemic infections.[6] The only cutaneous disease, *Pityriasis versicolor*, is purely correlated with the presence of *Malassezia*.[7–9] In other dermatological disorders, the fungi play only secondary but important roles either as an infectious agent or as a trigger.[10] *Malassezia* fungi comprise a group of 14 species,[11] while eight members of this group with pathological potential, including *Malassezia furfur*, have been isolated from human skin.[5]

Seborrheic dermatitis is the very common chronic inflammatory skin disease whose pathophysiological aspects are still poorly understood.[12] *Malassezia* species, *Malassezia furfur* in particular, has been associated with the progression and the degree of severity of this disease.[13] However, it was postulated that certain immunological conditions lead to over-colonisation of *Malassezia furfur* and that this induces an abnormal host inflammatory response that correlates with non-effective clearance of the skin microbes.[10,14] These factors accelerate epidermal or sebaceous abnormalities. Moreover, not only skin diseases are attributed to *Malassezia*. The fungi can cause systemic infections in severely immunocompromised patients and in preterm infants admitted to intensive care units.[15,16]

The most commonly used treatment against *Malassezia*-related dermatological disorders is a combination of the topical antifungal and anti-inflammatory drugs.[12,17] Together with these agents, additional therapeutic approaches are available for physicians including lithium gluconate/succinate, coal tar, salicylic acid, selenium sulfide, sodium sulfacetamide, glycerin, benzoyl peroxide, aloe vera, mud treatment, phototherapy, and phytotherapy.[10,18,19] Sulfonamides represent an important class of drugs.[20–23] However, their antifungal activity against *Malassezia furfur* has not yet been reported.

Here we report the synthesis and biological activity evaluation of several novel sulfonamides **6a–d** (Scheme 1) towards



Scheme 1 *Reagents and conditions*: i, MeOH, $SOCl_2$, 0 → 25 °C, then reflux, 2 h; ii, Ac_2O, Et_3N, DMAP (cat.), THF, 25 °C, overnight; iii, HNO_3, conc. H_2SO_4, 0 → 25 °C, then 25 °C, 30 min; iv, $Ba(OH)_2$, MeOH–H_2O, reflux, 18 h; v, MeOH, H_2SO_4 (cat.), 25 °C, sonication, 91 h; vi, $NaNO_2$, conc. HCl/water, 0 °C, 15 min; vii, SO_2, CuCl (cat.), HCl (aq.), –5 °C, then 0 °C, 75 min; viii, R^1R^2NH, CH_2Cl_2, 25 °C, overnight.

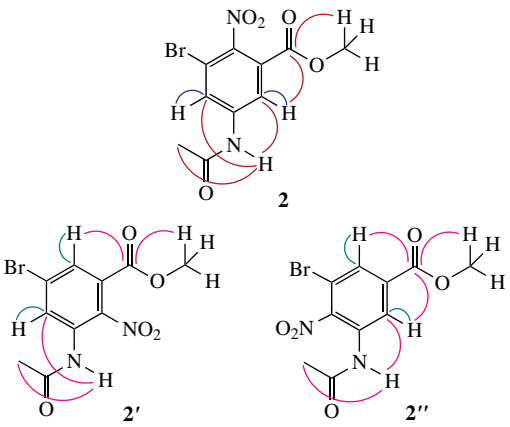


Figure 1 Structure determination of the relevant experimental (for **2**) and theoretical (for **2′** and **2″**) HMQC (blue) and HMBC (red) ^{1}H–^{13}C correlations in isomeric mono-nitro 5-acetamido-3-bromobenzoates.

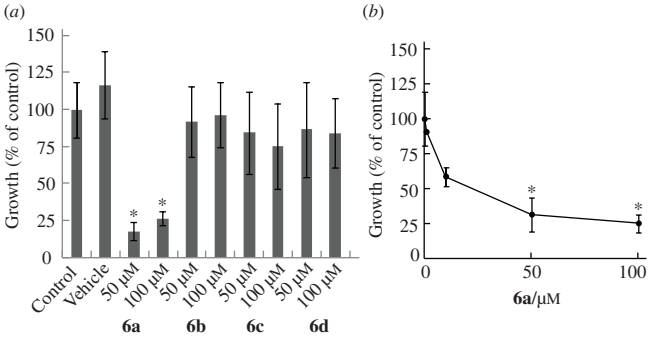


Figure 2 The impact of compounds on *Malassezia furfur* growth. *Malassezia furfur* was treated with the indicated concentration of the compounds or vehicle (DMSO). (*a*) Growth was determined fluorescently, as described in the experimental section. (*b*) The dose-response (1–100 μM) of compound **6a**, $n = 3$, $^{*}p < 0.05$.

Malassezia furfur viability. Arenesulfonamides bearing in benzene ring a combination of any type of carbonyl functionality, any halogen substituent and nitro group have been scarcely explored to date. To the best of our knowledge, only a few derivatives of 4-chloro (or -bromo)-2-nitro-5-sulfamoylbenzoic acid, described as early as 1955,[24] were later reported as advanced intermediates in the syntheses of patented diuretics,[25] anti-arrhythmics and Na-channel blockers,[26] as well as some specialty chemicals.[27,28]

In the synthesis of the novel 3-bromo-2-nitro-5-sulfamoylbenzoic acid derivatives **6a–d**, commercially available inexpensive 3-amino-5-bromobenzoic acid **1** was used as the starting material (see Scheme 1). Its esterification[29,30] and N-acetylation[29,31] was performed traditionally. Further nitration can in principle afford a mixture of isomers **2**, **2′** and **2″** (Figure 1). According to the reported data,[32,33] the use of conc. HNO_3 gave an equimolar **2**/**2′** mixture while application of conventional nitrating mixture (HNO_3–H_2SO_4) cleanly produced isomer **2**. In our hands, such a processing yielded individual mono-nitro derivative **2** in 70% yield. Its structure was unambiguously confirmed by 1D (^{1}H, ^{13}C/DEPT) and 2D (COSY, HMQC and HMBC) NMR experiments (see Figure 1) as well as the negative mode HRMS. The HMBC spectrum (in DMSO-d_6) revealed intensive cross-peaks between a broadened singlet of acetamide proton at 10.65 ppm with a signal of carbon of *N*-acetyl fragment at 24.2 ppm and with two protonated three-bond distanced aromatic carbon atoms $C^{4}H$ at 125.9 and $C^{6}H$ at 119.5 ppm. Additionally, in the HMBC spectrum, only the $C^{6}H$ proton at 8.18 ppm and the methoxy-group protons at 3.87 ppm exhibited an intensive three-bond correlation with the carbonyl carbon of the methoxycarbonyl moiety at 162.3 ppm. As shown in Figure 1, in the HMBC spectra of alternative mono-nitro isomers **2′** and **2″**, just one three-bond correlation between the acetamido-proton and the protonated aromatic carbons could be theoretically observed.

In contrast to the reported selective deacetylation of the acetyl amino-group in **2′** without cleavage of the methyl ester functionality,[33] our attempts to similarly deprotect amino group in compound **2** failed. Consequently, methyl 5-acetamido-3-bromo-2-nitrobenzoate **2** was exhaustively hydrolysed to anilino acid (86%) and, instead of the earlier reported O-methylation with potentially explosive diazomethane,[32] it was esterified with methanol under acidic catalysis and sonication to afford anilino ester **3** (62%).[34] Without sonication the esterification proceeded poorly (the yields were 10–20%). Further on, the anilino group was replaced with a sulfonyl chloride moiety using a modification[35] of the conventional Meerwein method.[36] For this purpose, anilino ester **3** was converted to diazonium salt **4** which was added to a cold concentrated aqueous solution of SO_2 and HCl[35] in the presence of a cuprous chloride catalyst. This afforded polyfunctionalized sulfonyl chloride **5** of *ca.* 70% purity, which could be used crude. Its reactions with aniline, diethylamine, piperidine and morpholine furnished the final sulfonamides **6a–d**, respectively.

The ability of these four compounds to inhibit the growth rate of *Malassezia furfur* was tested *in vitro*. Compound **6a** showed a significant cytotoxic effect in the pharmacological concentration for a topical application (50 μM) in which ~80% of the fungi were killed [Figure 2(*a*),(*b*)]. All other compounds were not active. Compound **6a** is the only secondary sulfonamide among all tested molecules, with its aniline moiety being the most lipophilic compared to amine ones of compounds **6b–d**. Thus, we hypothesized that these two important issues, namely, the presence of the less steric hindrances near the sulfonamide S–N bond and the high lipophilicity of the aniline may be responsible for the cytotoxic activity of compound **6a** and the lack of activity of other compounds.

In summary, several novel tetrasubstituted benzenesulfonamides **6a–d** were synthesized. One of the congeners, namely, methyl 3-bromo-2-nitro-5-(*N*-phenylsulfamoyl)benzoate **6a**, revealed an impressive antifungal cytotoxic activity (around 80% at 50 μM). This is the first report regarding a sulfonamide-based compound that is active against *Malassezia furfur.* The structural motif of **6a** may be used as a lead for the development of drug candidates against seborrheic dermatitis and probably some other skin diseases caused by the fungi.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.11.006.

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