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Synthesis of New Bengazole Analogues and Their Antimicrobial Activity

Jürgen KRAUSS*, Sandra KALKBRENNER, Angela SCHUSTER, Anne OBAINOKE, Franz BRACHER

Department of Pharmacy – Centre for Drug Research. Ludwig-Maximilians-University, Butenandtstr. 5-13, 81377 Munich-GERMANY

e-mail: hjkra@cup.uni-muenchen.de

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Bengazole A and bengazole B are 2 representatives out of a large family of marine metabolites isolated from a *Jaspis* sponge and display potent anti-fungal and anthelmintic activity as well as modest cytotoxic activity. This paper reports a short and efficient synthesis and microbiological evaluation of some new bengazole analogues.

Key Words: Bengazole, lithiation, antimicrobial activity, cytotoxicity.

Introduction

Bengazole A and bengazole B (Figure 1) were originally isolated in 1988 by Crews and co-workers from a sponge of the genus *Jaspis* and to date the bengazole family consists of more than 20 members.[1] The compounds display potent ergosterol dependent antifungal activity comparable to that of amphotericin B against *Candida albicans* and are active against fluconazole-resistant *Candida* strains. Furthermore, bengazole A shows full anthelmintic activity against the nematode *Nippostrongylus braziliensis* at just 50 μg/mL.[2,3]

Results and Discussion

Bengazole A is a potent antifungal lead, but its total synthesis is long and expensive.[4,5] Therefore, synthesis of more simple analogues is an interesting way of developing new antimycotic drugs. In continuation of our research on bengazole analogues,[6] furan-2-carbaldehyde was reacted with pent-4-enyl magnesium bromide in a Grignard reaction to give the corresponding racemic secondary alcohol **1**[7] whose hydroxyl group was protected as *tert.* butyl dimethyl silyl ether to give **2** (Scheme 1). The silyl ether **2** was lithiated with one equivalent of n-butyl lithium and benzene carbaldehyde was added to give the resulting alcohol **3**.[7,8] **3** was

*Corresponding author

esterified with octanoyl chloride to the ester **4** and subsequent cleavage of the silyl ether with tetrabutyl ammonium fluoride led to the target compound **5**.

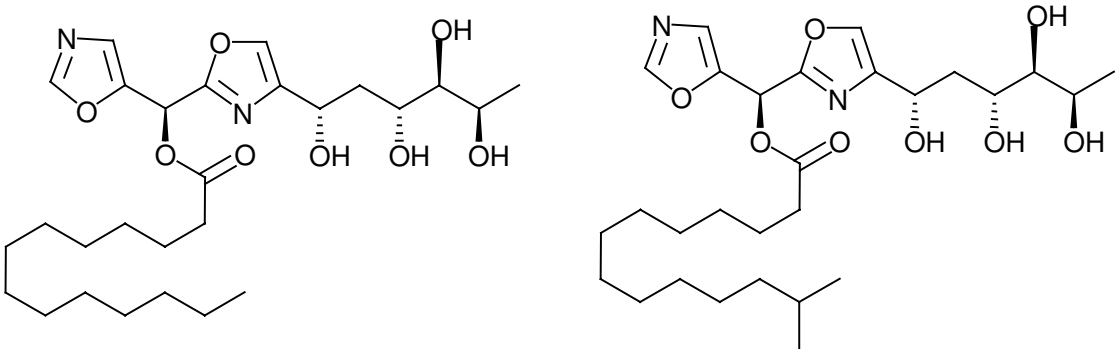
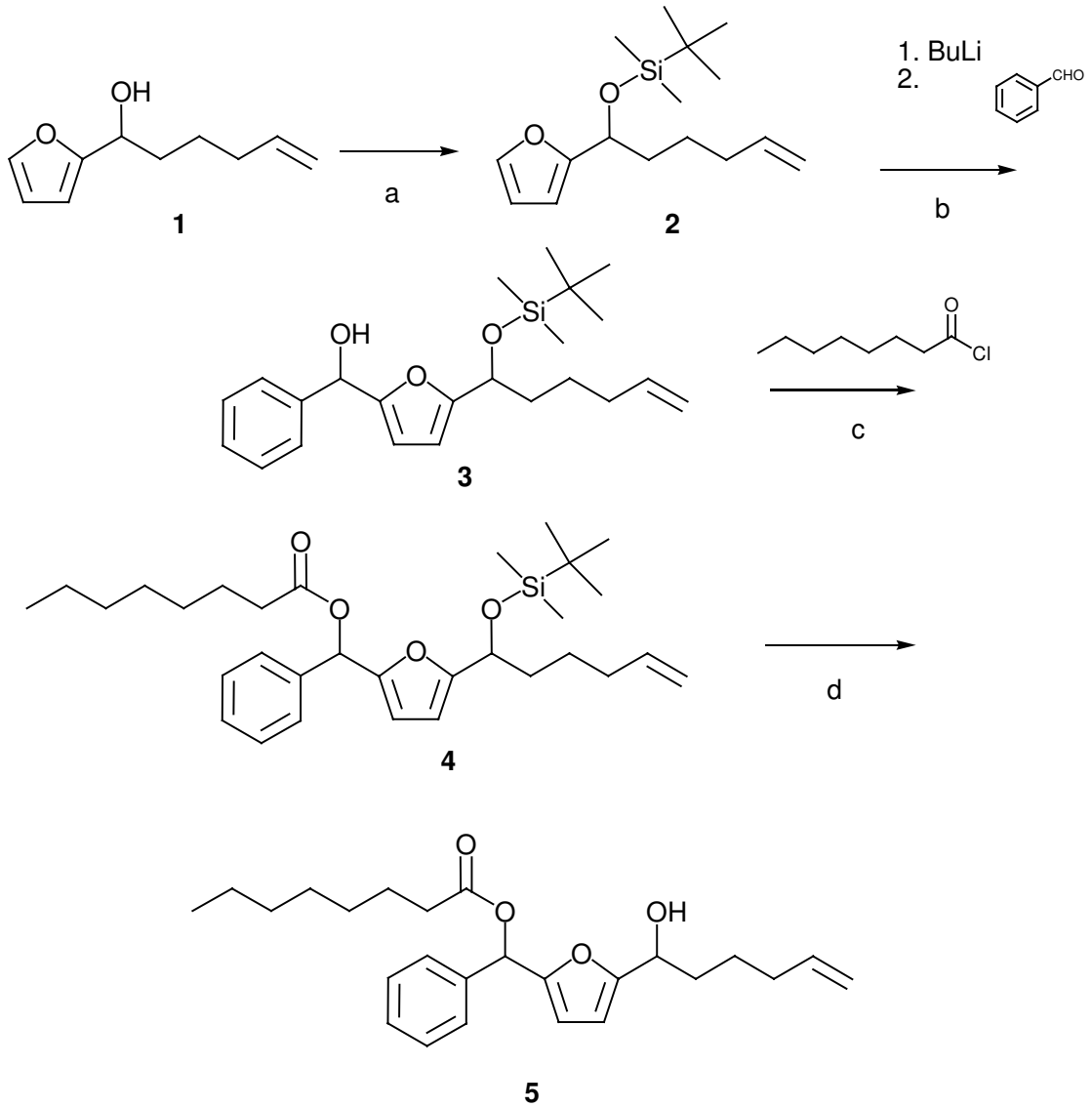
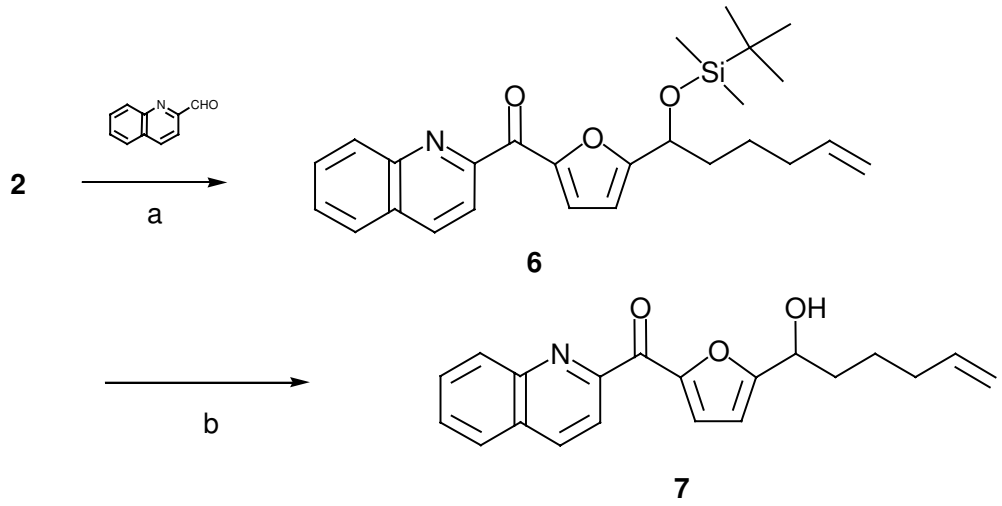


Figure 1. Structures of bengazole A and bengazole B.



Scheme 1. THF, TBDSCl, imidazole b. THF, –40 °C, c. toluene, NEt_3, d: THF, NBu_4F.

Using the same route quinoline-2-carbaldehyde was added to the lithiated silyl ether **2** (Scheme 2) but unexpectedly the ketone **6** was isolated as the main product instead of the alcohol. Cleavage of the silylether with tetrabutyl ammonium fluoride gave the hydroxyl ketone **7**.



Scheme 2. THF, –40 °C, BuLi. b. THF, NBu_4F.

The antimicrobial activity of the resulting compounds was determined in an agar diffusion assay and the results were compared with those of tetracycline, clotrimazol, and benzyl penicillin. The compounds exhibit only low or no activity against bacteria and fungi, as shown in Table 1.

Table 1. Agar diffusion assay (100 μg/disc, diameter of inhibition [mm]), bp: benzyl penicillin, te: tetracycline, cl: clotrimazol (50 μg/disc).

	3	**4**	**5**	**6**	**7**	**bp**	**cl**	**te**
Escherichia coli	0	0	0	0	0	7	nt	35
Pseudomonas antimicrobia	0	**6**	**10**	0	**8**	50	nt	25
Staphylococcus equorum	0	0	0	0	0	35	nt	35
Streptococcus entericus	**9**	**7**	**6**	0	0	40	nt	35
Candida glabrata	**7**	**8**	**8**	0	**8**	50	14	nt
Aspergillus niger	0	0	0	0	0	0	14	nt
Yarrowia lipolytica	0	0	0	0	0	0	20	nt
Hypopichia burtonii	0	0	0	0	0	0	25	nt

The cytotoxicity of the compounds **5** and **7** was determined in an MTT test[9] on HL 60 cells and the results were compared with those of cisplatin. Both compounds showed moderate cytotoxicity.

Table 2. MTT assay, IC_{50}: 50% inhibition of growth.

compounds	IG_{50} [μM]
5	150
7	110
Cisplatin	5

Experimental

IR-spectra: Perkin-Elmer FT-IR Paragon 1000; MS: Hewlett Packard MS-Engine, electron ionisation (EI) 70 eV, chemical ionisation (CI) with CH_4 (300 eV); NMR (400 MHz): Jeol GSX 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz); GLC-MS: Shimadzu GC 17 A; flash column chromatography (FCC): silica gel 60 (230 – 400 mesh, E. Merck, Darmstadt).

Agar diffusion assay: The bacteria and fungi were cultivated on an AC agar (Sigma), *Aspergillus niger* on a potato dextrose broth agar (Sigma). The substances were placed on 6 mm paper discs on the agar each impregnated with 100 μg of the tested compound or 50 μg of the reference drugs. The bacteria media were incubated for 24 h at 32 °C, the fungi media for 48 h at 28 °C, and the diameter of the zone of inhibition [mm] was registered.

tert-Butyl-(1-furan-2-yl-hex-5-enyloxy)-dimethyl-silane (2)

4.19 g (25.2 mmol) 1-furan-2-ylhex-5-en-1-ol (**1**) was dissolved in 20 mL of dry THF, and 4.54 g (30.2 mmol) of TBDS-chloride and 2.05 g (30.2 mmol) of imidazole were added. The solution was stirred under N_2 atmosphere for 12 h, the solvent was evaporated, the residue dissolved in 25 mL of water and extracted with diethyl ether (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated and the residue was purified by flash column chromatography (n-hexane/ethyl acetate 10:1) to give 5.0 g (70.7%) of **2** as a colourless oil. Elemental analysis $C_{16}H_{28}O_2Si$ (280.49). ^{1}H-NMR ($CDCl_3$) δ (ppm) = -0.07 (s, 3 H, CH_3), 0.05 (s, 3 H, CH_3), 0.87 (s, 9 H, 3 CH_3), 1.43 (m, 2 H, CH_2), 1.79 (m, 2 H, CH_2), 2.06 (m, 2 H, CH_2), 4.66 (m, 1 H, CH), 4.94 (m, 1 H, =CH_2), 4.99 (m, 1 H, =CH_2), 5.79 (ddt, J = 6.8 Hz, J = 10.2 Hz, J = 17.2 Hz, 1 H, -CH=), 6.15 (d, J = 3.3 Hz, 1 H, aromat. CH), 6.29 (dd, J = 1.7 Hz, J = 3.3 Hz, 1 H, aromat. CH), 7.33 (dd, J = 0.8 Hz, J = 1.7 Hz, 1 H, aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = -5.09 (CH_3), -4.89 (CH_3) 18.23 (quart. C), 24.69 (CH_2), 25.81 (3 CH_3), 33.50 (CH_2), 36.42 (CH_2), (CH_2), 68.43 (CH), 105.57 (aromat. CH), 109.94 (aromat. CH), 114.51 (=CH_2), 138.74 (-CH=), 141.16 (aromat. CH), 157.46 (quart. C).

{5-[1-(*tert*-Butyl-dimethyl-silanyloxy)-hex-5-enyl]-furan-2-yl}-phenyl-methanol (3)

1.67 g (5.95 mmol) of **2** was dissolved in 20 mL of dry THF under N_2 atmosphere and cooled to –40 °C. Then 5 mL of 1.6 M BuLi in n-hexane solution was added dropwise and the mixture was allowed to warm up to –10 °C. Then the solution was cooled to –40 °C again and 630 mg (5.9 mmol) of benzene carbaldehyde was added. The mixture was stirred for 12 h and allowed to warm up to room temperature. The solution was quenched with 20 mL of brine and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by flash column chromatography (n-hexane/ethyl acetate 5:1) to give 1.43 g (62.2%) of **3** as a pale yellow oil. Elemental analysis $C_{23}H_{34}O_3Si$ (386.61). Calcd.: C: 71.46. H: 8.86. S: 8.17. Found: C: 70.76. H: 9.32. MS (CI): m/z (%) = 387, (M^++1, 4), 369 (80), 255 (100), 237 (98). HR-MS (M^+ - OH): Calcd.: 369.2250. Found: 369.2281. ^{1}H-NMR ($CDCl_3$) δ (ppm) = -0.10 (m, 3 H, CH_3), 0.02 (m, 3 H, CH_3), 0.85 (m, 9 H, 3 CH_3), 1.42 (m, 2 H, 3-H), 1.77 (m, 2 H, 2-H), 2.04 (m, 2 H, 4-H), 4.64 (m, 1 H, 1-H), 4.97 (m, 2 H, 6-H), 5.77 (m, 1 H, 5-H), 5.79 (m, 1 H, CH), 6.01 (m, 1 H, aromat. CH), 6.08 (m, 1 H, aromat. CH), 7.36 (m, 5 H, 5 aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = -5.06 (CH_3), -4.85 (CH_3), 18.18 (quart. C), 24.65 (CH_2), 25.78 (3 CH_3), 33.47 (CH_2), 36.27 (CH_2), 68.39 (CH), 70.19 (CH), 106.16 (aromat. CH), 107.87 (aromat.

CH), 114.53 (=CH_2), 126.63 (2 aromat. CH), 127.94 (aromat. CH), 128.36 (2 aromat. CH), 138.70 (-CH=), 140.87 (quart. C), 154.69 (quart. C), 157.57 (quart. C).

Octanoic acid {5-[1-(*tert*-butyl-dimethyl-silanyloxy)-hex-5-enyl]-furan-2-yl}-phenyl-methyl ester (4)

200 mg (0.52 mmol) of **3** was dissolved in dry toluene, and 5 mL of triethyl amine and 120 mg (0.75 mmol) octanoyl chloride were added. The mixture was stirred for 6 h, the solvent was evaporated, and the residue dissolved in 20 mL of water. The suspension was extracted with diethyl ether (3 × 30 mL), the combined organic layers were dried over Na_2SO_4, the solvent was evaporated, and the residue was purified by flash column chromatography (n-hexane/ethyl acetate 7:1) to give 194 mg (73.0%) of **4**. Elemental analysis $C_{31}H_{48}O_4Si$ (512.81). MS (EI): m/z (%) = 455 (M^+-57, 76), 311 (100). HR-MS (M^+-57): Calcd.: 455.2618. Found: 455.2587. ^{1}H-NMR ($CDCl_3$) δ (ppm) = -0.11 (m, 3 H, CH_3), 0.02 (m, 3 H, CH_3), 0.85 (m, 9 H, 3 CH_3), 0.87 (m, 3 H, CH_3), 1.26 (m, 8 H, 4 CH_2), 1.69 (m, 6 H, 3 CH_2), 2.04 (m, 2 H, CH_2), 2.37 (m, 2 H, CH_2), 6.62 (m, 1 H, 1-H), 4.96 (m, 2 H, 6-H), 5.77 (m, 1 H, 5-H), 6.07 (m, 2 H, 2 aromat. CH), 6.84 (s, 1 H, CH), 7.35 (m, 5 H, 5 aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = -5.08 (CH_3), -4.88 (CH_3), 14.04 (CH_3), 18.03 (quart. C), 22.57 (CH_2), 24.60 (CH_2), 24.63 (CH_2), 25.78 (3 CH_3), 29.98 (CH_2), 30.12 (CH_2), 31.64 (CH_2), 34.55 (CH_2), 35.53 (CH_2), 37.25 (CH_2), 68.24 (CH), 70.37 (CH), 106.03 (aromat. CH), 109.95 (aromat. CH), 114.52 (=CH_2), 127.18 (2 aromat. CH), 128.20 (aromat. CH), 128.37 (2 aromat. CH), 137.66 (quart. C), 138.69 (-CH=), 151.11 (quart. C), 158.18 (quart. C), 172.68 (CO).

Octanoic acid [5-(1-hydroxy-hex-5-enyl)-furan-2-yl]-phenyl-methyl ester (5)

150 mg (0.3 mmol) of **4** was dissolved in 5 mL of dry THF and 2 mL of a 1 M solution of NBu_4F in THF was added. The mixture was stirred for 12 h at room temperature, the solvent was evaporated, and the residue was dissolved in 20 mL of water. The suspension was extracted with diethyl ether (3 × 30 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography (n-hexane/ethyl acetate 5:1) to give 90 mg (75.0 mg) of **5**. Elemental analysis $C_{25}H_{34}O_4$ (398.55) MS (EI): m/z (%) = 398 (M^+, 4), 255 (100). HR-MS: Calcd.: 398.2457. Found: 398.2451. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 0.87 (t, J = 6.8 Hz, 3 H, CH_3), 1.26 (m, 10 H, 5 CH_2), 1.63 (m, 2 H, CH_2), 1.82 (m, 2 H, CH_2), 2.07 (m, 2 H, CH_2), 2.38 (t, J = 7.3 Hz, 2 H, CH_2), 4.64 (m, 1 H, CH), 4.95 (m, 1 H, =CH_2), 5.00 (m, 1 H, =CH_2), 5.78 (m, 1 H, -CH=), 6.08 (m, 1 H, aromat. CH), 6.16 (d, J = 2.9 Hz, 1 H, aromat. CH), 6.85 (s, 1 H, CH), 7.35 (m, 5 H, 5 aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 14.07 (CH_3), 22.60 (CH_2), 24.72 (CH_2), 24.93 (CH_2), 29.02 (CH_2), 31.66 (CH_2), 33.42 (CH_2), 34.44 (CH_2), 34.87 (CH_2), 34.92 (CH_2), 67.62 (CH), 70.34 (CH), 106.33 (aromat. CH), 110.16 (aromat. CH), 114.79 (=CH_2), 127.20 (2 aromat. CH), 128.36 (aromat. CH), 128. 47 (2 aromat. CH), 137.50 (quart. C), 138.45 (-CH=), 151.82 (quart. C), 158.00 (quart. C), 172.72 (CO).

{5-[1-(*tert*-Butyl-dimethyl-silanyloxy)-hex-5-enyl]-furan-2-yl}-quinolin-2-yl-methanone (6)

The compound was prepared as described for **3** from 1.67 g (5.95 mmol) of **2** and 0.94 g (6.0 mmol) of quinoline-2-carbaldehyde to give 1.48 g (57%) of **6**. Elemental analysis $C_{26}H_{33}NO_3Si$ (435.64) Calcd.: C: 71.68. H: 7.64. N: 3.22. Found.: C: 70.77. H: 7.48. N: 3.22. MS (CI): m/z (%) = 436, (M^++1, 100), 378 (30), 304 (84). HR-MS: Calcd.: 435.2230. Found: 435.2223. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 0.02 (s, 3 H, CH_3), 0.10 (s, 3 H, CH_3), 0.92 (s, 9 H, 3 CH_3), 1.50 (m, 2 H, 3'-H), 1.86 (m, 2'-H), 2.08 (m, 2 H, 4'-H), 4.91

(t, J = 6.1 Hz, 1 H, 1'-H), 4.95 (m, 1 H, 6'-H), 5.00 (m, 1 H, 6'-H), 5.79 (ddt, J = 6.6 Hz, J = 10.4 Hz, J = 17.1 Hz, 1 H, 5'-H), 6.50 (d, J = 3.4 Hz, 1 H, 4"-H), 7.66 (m, 1 H, aromat. CH), 7.81 (m, 1 H, aromat. CH), 7.90 (d, J = 8.2 Hz, 1 H, aromat. CH), 8.23 (m, 3 H, 3 aromat. CH), 8.33 (d, J = 8.5 Hz, 1 H, aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = -5.05 (CH_3), - 4.81 (CH_3), 18.18 (quart. C), 24.20 (CH_2), 25.78 (3 CH_3), 33.50 (CH_2), 36.87 (CH_2), 68.20 (CH), 108.46 (aromat. CH), 114.68 (=CH_2), 120.02 (aromat. CH), 126.27 (aromat. CH), 127.73 (aromat. CH), 128.43 (aromat. CH), 129.21 (quart. C), 130.08 (aromat. CH), 130.42 (aromat. CH), 136.98 (aromat. CH), 138.54 (-CH=), 146.92 (quart. C), 150.01 (quart. C), 153.89 (quart. C), 164.98 (quart. C), 178.92 (CO).

[5-(1-Hydroxy-hex-5-enyl)-furan-2-yl]-quinolin-2-yl-methanone (7)

The compound was prepared as described for **5** from 500 mg (1.15 mmol) of **6** to give 280 mg (76%) of **7**. Elemental analysis $C_{20}H_{19}NO_3$ (321.38). ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.53 (m, 1 H, 3-H), 1.63 (m, 1 H, 3-H), 1.94 (m, 2 H, 2-H), 2.12 (m, 2 H, 4-H), 3.47 (s, 1H, OH), 4.87 (m, 1 H, 1-H), 4.95 (m, 1 H, 6-H), 5.02 (m, 1 H, 6-H), 5.80 (ddt, J = 6.5 Hz, J = 10.3 Hz, J = 17.0 Hz, 1 H, 5-H), 6.54 (d, J = 3.6 Hz, 1 H, 4'-H), 7.65 (m, 1 H, aromat. CH), 7.78 (m, 1 H, aromat. CH), 7.86 (d, J = 8.6 Hz, 1 H, aromat. CH), 8.19 (m, 3 H, 2 aromat. CH), 8.29 (d, J = 8.2 Hz, 1 H, aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 24.59 (CH_2), 33.42 (CH_2), 35.23 (CH_2), 67.84 (CH), 108.46 (aromat. CH), 114.88 (=CH_2), 119.91 (aromat. CH), 126.26 (aromat. CH), 127.71 (aromat. CH), 128.53 (aromat. CH), 129.20 (quart. C), 130.13 (aromat. CH), 130.37 (aromat. CH), 137.04 (aromat. CH), 138.36 (-CH=), 146.85 (quart. C), 150.19 (quart. C), 153.55 (quart. C), 163.90 (quart. C), 179.10 (CO).

Conclusion

The synthesis describes a short and efficient way to obtain analogues of bengazole A. The antibiotic, antimycotic, and cytotoxic activities of the resulting compounds are only weak and far from those of the natural products or common used drugs.

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References

1. M. Adamczeski, E. Quinoa and P. Crews, **J. Am. Chem. Soc. 110**, 1598 (1988).
2. R. Fernandez, M. Dherbomez, Y. Letourneux, J.F. Verbist and J.F. Biard, **J. Nat. Prod. 62**, 678-680 (1999).
3. A. Groweiss, J.J. Newcomer, B.R. O'Keefe, A. Blackman and M.R. Boyd, **J. Nat. Prod. 62**, 1691-1693 (1999).
4. R.J. Mulder, C.M. Shafer and T.F. Molinski, **J. Org. Chem. 64**, 4995-4998 (1999).
5. J.A. Bull, E.P. Balskus, R.A.J. Horan, M. Langner and S.V. Ley, **Chem. Eur. J. 13**, 5515-5538 (2007).
6. J. Krauss and D. Unterreitmeier, **Arch. Pharm. Med. Chem. 335**, 94-98 (2002).
7. J. Krauss, D. Unterreitmeier and D. Antlsperger, **Arch. Pharm. Pharm. Med. CHEM 336**, 381-384 (2003).
8. J. Krauss and D. Unterreitmeier, **Arch. Pharm. Pharm. Med. Chem. 338**, 44-48 (2005).
9. T.J. Mosmann, **Immunol. Methods 65**, 55-63 (1983).