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OPPI BRIEF



# Novel Antimicrobial Sulfonamides Derived from Nabumetone

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Throughout the last decade, novel Mannich bases have served as important sources of new drug candidates.[1–6] These have been evaluated as potential treatments for a multitude of diseases and medical conditions as prodrugs, or as molecules eliciting responses from specific biological targets.[7–9] Nabumetone (Figure 1) is an inexpensive readily-available non-steroidal anti-inflammatory drug (NSAID) with well-defined activity and toxicity profiles.[5–8] Since it is a methyl ketone, we felt that it would be a useful starting material for Mannich reactions aimed at preparing a new category of sulfonamide antibacterials. The present work is a pilot study directed toward the building of novel Mannich bases derived from nabumetone and the well-documented sulfa drug sulfamethoxazole (Figure 2).[8]

In the event, compounds **1**-**4** were prepared by reaction of nabumetone with aromatic aldehydes and sulfamethoxazole in a straightforward procedure (Scheme 1; see Experimental section), leading to the desired Mannich bases. Sulfonamides in general have reduced nucleophilicity due to the electron-withdrawing capability of the sulfonyl moiety, and sometimes they do not undergo reactions typical of primary amines. We were thus pleased to note that our procedure led to the desired bases in moderate to good yields (mean 70%), typical for the Mannich process. The products were obtained in pure form. The novel Mannich bases could be readily identified on the basis of their characteristic spectra. Thus, the FTIR data of compounds **1**-**4** showed the appearance of absorption bands near 3400-3344 $cm^{-1}$ for NH, 3080 $cm^{-1}$ for C-H (aromatic), 1710 $cm^{-1}$ for C = O, 1340 and 1160 $cm^{-1}$ for $SO_2$. In addition, we observed the disappearance of the two bands near 3300 $cm^{-1}$ for $NH_2$. The spectrometric data are more extensively listed in Table 1 and microanalysis data are listed in Table 2.

The compounds showed significant activity against gram-positive and gram-negative bacteria. These results are gathered in Table 3. We used the well diffusion method to assess the activities of our new sulfonamides, based on zones of inhibition versus controls. Sulfamethoxazole was used as a positive control, and it showed strong activity; while DMSO was used as negative control and showed no inhibition. Compound **1** showed strong inhibition against all types of bacteria in all the concentrations used.

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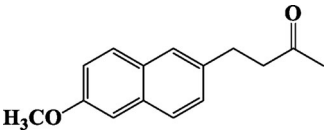


Figure 1. Nabumetone.

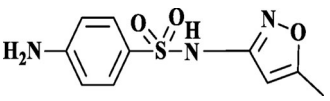
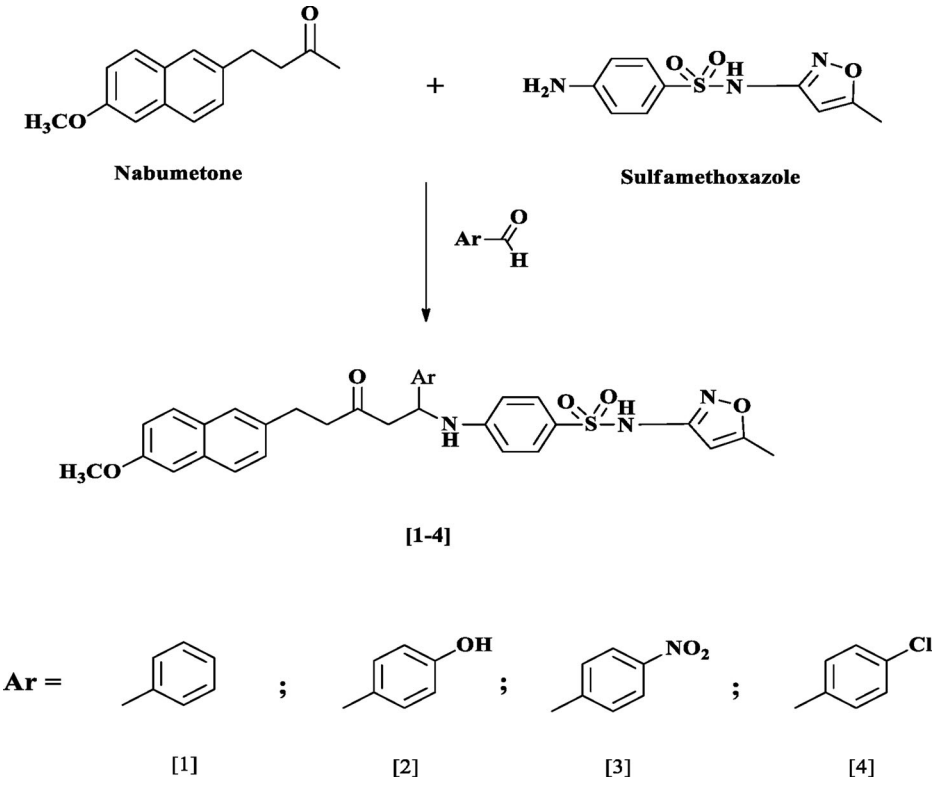


Figure 2. Sulfamethoxazole.




Scheme 1. Preparation of novel sulfonamides (EtOH/$CHCl_3$ 3/1, HCl, 25 h, 25 °C).

Compound **2** showed strong activity against *Pseudomonas aeruginosa* and moderate inhibition against *Acinetobacter species* and *Streptococcus pyogenes*, while no inhibition against *Staphylococcus aureus* was observed. Compound **3** showed strong activity against *S. aureus,* moderate activity against *Acinetobacter species, S. pyogenes* and *P. aeruginosa.* Finally, compound **4** showed strong activity against *P. aeruginosa* and weak activity against *Acinetobacter species, S. pyogenes* and no inhibition against *S. aureus.*

In conclusion, novel Mannich bases were prepared from nabumetone and sulfamethoxazole. The compounds were obtained in pure form in a method noteworthy for its simplicity. Antimicrobial activities were determined against several bacterial strains. It is

**Table 1.** Preparation of Mannich derivatives.

| Products & reactants | Time (h) | Yield (%) | m.p (°C) | IR ($cm^{-1}$) | $^1H$ NMR ($\delta$) |
|---|---|---|---|---|---|
| 1 | 25 | 77 | 124-126 | 3396, 3080, 2899, 2860, 1710, 1346, 1159 | 2.29 (s, 3H, $CH_3$), 2.52 (m, 2H, $CH_2$), 2.85-3.10 (m, 4H, $CH_2$-$CH_2$), 3.40 (s, 3H, $OCH_3$), 4.94-5.01 (CH), 6.11 (C = C-H), 6.61 (NH), 7.19-7.76 (aromatic ring), 11.01 (s, 1H, NH-$SO_2$) |
| 2 | 25 | 63 | 96-98 | 3400, 3097, 2983, 2856, 1712, 1348, 1159 | 2.29 (s, 3H, $CH_3$), 2.75 (d, 2H, $CH_2$), 2.88-2.97 (m, 4H, $CH_2$-$CH_2$), 3.42 (s, 3H, $OCH_3$), 4.84 (m, 1H, CH), 6.11 (s, 1H, C = C-H), 6.60-6.63 (m, 1H, NH), 7.09-7.77 (aromatic ring), 9.34 (s, 1H, OH), 11.00 (s, 1H, NH-$SO_2$) |
| 3 | 27 | 85 | 200-202 | 3379, 3076, 2931, 2847, 1708, 1344, 1159 | 2.28 (s, 3H, $CH_3$), 2.52 (d, 2H, $CH_2$), 2.87-3.80 (m, 4H, $CH_2$-$CH_2$), 3.86 (s, 3H, $OCH_3$), 5.00-5.13 (m, 1H, CH), 6.12 (s, 1H, C = C-H ), 6.64-6.78 (d, 1H, NH), 7.13-8.26 (aromatic ring), 11.05 (s, 1H, NH-$SO_2$) |
| 4 | 22 | 58 | 186-188 | 3344, 3087, 2939, 2843, 1703, 1338, 1161 | 2.52 (s, 3H, $CH_3$ & d, 2H, $CH_2$), 2.85-3.05 (m, 4H, $CH_2$-$CH_2$), 3.86 (s, 3H, $OCH_3$), 4.98-6.05 (m, 1H, CH), 6.59-6.63 (s, 1H, C = C-H & d, 1H, NH), 7.11-8.48 (aromatic ring), 11.37 (s, 1H, NH-$SO_2$) |
| Nabumetone | – | – | 80-83 | 3053, 3009, 2955, 2901, 2837, 1707 | 2.12 (s, 3H, $CH_3$), 2.82-2.95 (m, 4H, $CH_2$-$CH_2$), 3.87 (s, 3H, $OCH_3$), 7.13-7.76 (aromatic ring) |
| Sulfamethoxazole | – | – | 167 | 3468, 3375, 3298, 3144, 2931, 1369, 1143 | 2.30 (s, 3H, $CH_3$), 6.01 (CH isoxazole ring), 6.5 ($NH_2$), 7.21-7.76 (aromatic ring), 11.55(s, 1H, NH-$SO_2$). |

**Table 2.** Elemental analyses of new compounds.

| Product | Molecular formula | Anal. Calcd. | Found |
|---|---|---|---|
| 1 | $C_{32}H_{31}N_3O_5S$ | C, 67.47; H, 5.48; N, 7.38 | C, 67.40; H, 5.53; N, 7.30 |
| 2 | $C_{32}H_{31}N_3O_6S$ | C, 65.62; H, 5.34; N, 7.17 | C, 65.68; H, 5.37; N, 7.21 |
| 3 | $C_{32}H_{30}N_4O_7S$ | C, 62.53; H, 4.92; N, 9.11 | C, 62.58; H, 4.88; N, 9.16 |
| 4 | $C_{32}H_{30}N_3O_5SCl$ | C, 63.62; H, 5.01; N, 6.96 | C, 63.54; H, 5.04; N, 7.03 |

our hope that our convenient method of preparation in moderate to good yields will foster further exploration of these potentially useful sulfonamide derivatives.

## Experimental section

Some related 4-((1-(4-substitutedphenyl)-5-(6-methoxynaphthalen-2-yl)-3-oxopentyl)amino)-N-(5-methylisoxazol-3-yl)benzenesulfonamide derivatives had been synthesized previously.[11] Our anti-bacterial activity tests were conducted in accordance with the well-diffusion method.[12–13] All chemicals were supplied by BDH, Fluka and Sigma Aldrich chemical companies. Mueller Hinton Agar was supplied from Salucea while

**Table 3.** Anti-microbial activity of the prepared compounds.

| | | Zone of inhibition (mm) | | | |
|---|---|---|---|---|---|
| | | Gram negative | | Gram positive | |
| Sample code and standard | Concentration (μg/ml) | *Acinetobacter species* | *Pseudomonas aeruginosa* | *Streptococcus pyogenes* | *Staphylococcus aureus* |
| 1 | 500.0 | 17 | 15 | 15 | 17 |
| | 250.0 | 15 | 15 | 13 | 15 |
| | 125.0 | 15 | 13 | 11 | 13 |
| | 62.5 | 13 | 11 | 11 | – |
| 2 | 500.0 | 11 | 21 | 10 | – |
| | 250.0 | 9 | 17 | 8 | – |
| | 125.0 | 9 | 15 | 8 | – |
| | 62.5 | 6 | 7 | 5 | – |
| 3 | 500.0 | 9 | 15 | 17 | 21 |
| | 250.0 | 5 | 13 | 13 | 17 |
| | 125.0 | 11 | 9 | 9 | 15 |
| | 62.5 | 5 | 7 | 9 | 7 |
| 4 | 500.0 | 5 | 21 | 7 | 7 |
| | 250.0 | 7 | 15 | 6 | – |
| | 125.0 | 9 | 11 | 4 | – |
| | 62.5 | 4 | 11 | 5 | – |
| Sulfamethoxazole | 500.0 | 20 | 10 | 20 | 20 |
| | 250.0 | 16 | 6 | 18 | 17 |
| | 125.0 | 16 | 6 | 16 | 14 |
| | 62.5 | 8 | 4 | 16 | 10 |
| DMSO | – | – | – | – | – |

Zone of inhibition: (-) no inhibition; (3-6) weak; (7-10) moderate; (11-21) strong.

blood agar base was supplied from HIMEDIA. Melting points in the experimental work were recorded through the use of Gallenkamp electro-thermal melting point apparatus and are uncorrected. Infrared spectra were recorded by using a Shimadzu 8400s instrument, as KBr discs. $^1$H-NMR (300 MHz) spectra were recorded on a Bruker Avance 300 instrument; DMSO-$d_6$ was used as a solvent. Elemental analyses were recorded on a Vario MICRO CUBE instrument.

### *Typical preparation*

Sulfamethoxazole (1 mmol) was added to a solution of an aromatic aldehyde (1 mmol) in a mixed solvent of anhydrous ethanol-chloroform (v/v = 3/1). This mixture was stirred, nabumetone (1 mmol) was added, followed by a few drops of concentrated hydrochloric acid as a catalyst. The mixture was stirred continuously for 22 to 27 h at 20–32 °C, then the suspension was chilled in the refrigerator overnight. The suspension was filtered; then the filter cake was washed with 95% ethanol. The resulting solid was suspended in water, adjusted to pH 7–8 with 10% $K_2CO_3$, and stirring was maintained for 2 h. The suspension formed was filtered, washed with cold water (2-5 mL) and absolute ethanol (2-3 mL), then dried overnight to yield the product.

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## References

1. D. Rosenbloom and M. A. Craven, *Canadian Family Physician*, 29, 2121 (1983).
2. I. Morita, *Prostaglandins & Other Lipid Mediators*, 68–69, 165 (2002). doi:10.1016/s0090-6980(02)00029-1
3. P. B. Rathi and K. V. Deshpande, *Asian J. of Biomed. and Pharmaceut. Sci*., 3, 30 (2013).
4. M. A. Gonzalo-Garijo, C. Cordobés-Dun, A. M. Lamilla-Yerga and I. Moreno-Gaston, *J. Investig. Allergol Clin. Immunol*., 17, 274 (2007).
5. N. V. Olsen, N. G. Jensen, J. M. Hansen, N. J. Christensen, N. Fogh-Andersen and I. Kanstrup, *Clin. Sci*., 97, 457 (1999).
6. S. Bala, N. Sharma, A. Kajal, S. Kamboj and V. Saini, *Int. J. Med. Chem.*, 1 (2014).
7. G. Bosica and R. Zammit, *PeerJ*, 1 (2018).
8. M. Mahdi, A. Raauf and S. Rzoqi, *Der Pharma Chemica*, 8, 424 (2016).
9. R. Bhardwaj, P. Parihar, K. Yadav and N. B. Bardhan, *Galore Int. J. Applied Sci. and Humanities*, 2, 19 (2018).
10. T. J. Sindhu, C. Meena and K. Krishnakumar, *Hygeia J. D. Med*., 10, 27 (2018).
11. W. Hang, Y. Ju-fang, S. Ziao-li, F. Li, X. Jin, Z. Guang-ming, J. Li and Y. Da-cheng, *Bioorg. & Med. Chem*., 20, 2119 (2012).
12. V. Kuete, K. O. Eyong, G. N. Folefoc, V. P. Beng, H. Hussain, K. Krohn and A. E. Nkengfack, *Pharmazie*, 62, 552 (2007).
13. N. L. Pfoze, Y. Kumar, B. Myrboh, R. K. Bhagobaty and S. R. Joshi, *J. of Med. Plants Res.,* 5, 859 (2011).