Kurzmitteilung:

Sydnone Derivatives: Synthesis and Antimicrobial Activity

Sydnon-Derivate: Synthese und Wirksamkeit gegen Mikroorganismen

H. Gülhan Pilli (Ayyildiz) and Cihat Şafak

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Hacettepe University, Ankara, Turkey

Ufuk Abbasoğlu

Department of Microbiology, Faculty of Pharmacy, Gazi University, Ankara, Turkey

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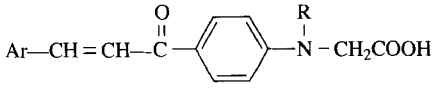
Amongst a number of mesoionic compounds studied so far, sydnones have attained importance due not only to their structural features and chemical properties, but also to their biological properties.

Sydnone derivatives have been extensively studied for their biological activities[1-3], the antimicrobial activity of substituted aryl sydnones has been reported[4-6]. Aryl sydnones are less toxic and more active than alkyl sydnones[7].

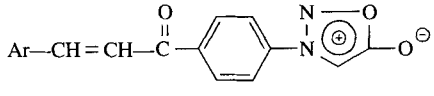
Also chalcone analogues are known to have antimicrobial activity[8-10].

Therefore, we synthesized compounds containing both sydnones and chalcone moieties (Table 1).

Table 1:



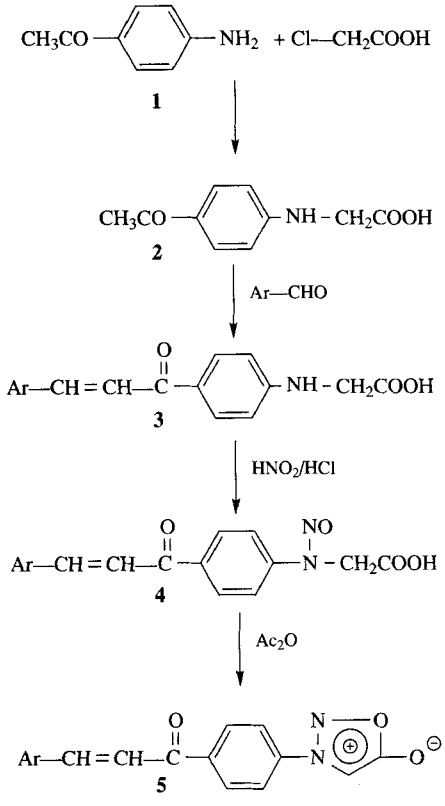
Comp.	R	Ar
3a	H	2-thienyl
4a	NO	
3b	H	2-pyridyl
4b	NO	
3c	H	3-pyridyl
4c	NO	
3d	H	4-pyridyl
4d	NO	



5a	2-thienyl
5b	2-pyridyl
5c	3-pyridyl
5d	4-pyridyl

N-(4-Acetylphenyl)glycine (**2**) was obtained from chloroacetic acid and 4-aminoacetophenone (**1**). By base catalyzed reaction of **2** with appropriate aromatic aldehydes, the corresponding 1,3-diaryl-2-propenones **3** were synthesized. *N*-nitrosation of **3** with nitrous acid at 0-5°C led to the nitroso derivatives **4** which were cyclized to the corresponding sydnones **5** (Scheme 1).

Yields, melting points, molecular formulae and analyses are listed in Table 2.



Scheme 1

Compound **5b** is known[11]; we synthesized it for the evaluation of its antibacterial and antifungal activities.

Table 3 lists the minimal inhibitory concentrations (MIC) of the compounds. Of the 1,3-diaryl-2-propenone derivatives compound **3d** was active against *Pseudomonas aeruginosa*. The other results of compounds **3a-d** were approximately identical. Of the nitroso derivatives especially **4b** was active against *Candida albicans* when compared to clotrimazole. None of the sydnones showed superior activity to references. The activity increased when the pyridyl ring was substituted by a thienyl ring. **5d** was more active when compared to other compounds against *Candida albicans*, *C. parapsilosis*, *C. pseudotropicalis*, and *C. stellatoidea*.

All the compounds were more active against *Gram(-)* bacteria than against *Gram(+)* bacteria when compared to ampicillin trihydrate.

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Experimental Part

Melting points: uncorrected, Thomas Hoover melting point apparatus. - IR spectra: (KBr, $\tilde{\nu}$ in cm^{-1}) Perkin Elmer 457 IR grating spectrophotometer. ^{1}H-NMR: Bruker AC 80 FT spectrometer, TMS as internal standard, [D_6]DMSO, (chemical shift in δ ppm). - Analytical data: Hewlett Packard 185 C, H, N, analyzer, Microanalysis Laboratory, Chemistry Department Middle East Technical University, Ankara/Turkey.

N-(4-Acetylphenyl)glycine

The compound was synthesized according to the lit.[6].

1,3-Diaryl-2-propenons (**3**)

To the mixture of equimolar (0.1 mole) amounts of *N*-(4-acetylphenyl)glycine (**2**) and appropriate aldehyde dissolved in 25 ml of ethanol, NaOH (10%) was added in portions to render the solution alkaline. The reaction mixture was stirred for 4 h at room temp. After neutralization with 10% HCl, the precipitate was filtered off and crystallized from benzene.

N-{4-[3-(4-Pyridyl)-2-propenoyl]phenyl}glycine (**3d**)

IR: 3350 (NH), 3200-2700 (OH), 1710 (CO), 1650 (CH=CH), 1600 (COO). - ^{1}H-NMR: 3.90 (s, 2H, CH_2), 6.65 (d, J = 2 Hz, 1H, CHCO), 7.50-7.90 (m, 9H, Ar-H, Ar-CH=).

Nitrosation

To the solution of 0.01 mole **3** in methanol, 20% HCl (20 ml) was added and the mixture was cooled to 0-5°C. Then a solution of $NaNO_2$ (0.011 mole) was added slowly with stirring. Stirring was continued for 4 h and the solid was filtered and crystallized from aq. ethanol.

Table 2: Yield %, melting point, molecular formula, and analysis of compounds **3** - **5**

Comp. No	Yield %	m.p. °C	Molecular Formula	Analysis % (Calc./Found) C	H	N
3a	60	135	$C_{15}H_{13}NO_3S$	62.70	4.56	4.87
				62.90	5.05	5.18
3b	61	205	$C_{16}H_{14}N_2O_3$	68.08	5.00	9.92
				67.91	4.80	9.63
3c	68	185	$C_{16}H_{14}N_2O_3$	68.08	5.00	9.92
				68.15	5.05	9.80
3d	65	189	$C_{16}H_{14}N_2O_3$	68.08	5.00	9.92
				67.83	5.30	9.89
4a	61	180	$C_{15}H_{12}N_2O_4S$	56.95	3.82	8.85
				56.91	3.86	8.73
4b	63	175	$C_{16}H_{13}N_3O_4$	61.73	4.21	13.50
				61.77	4.44	13.37
4c	70	142	$C_{16}H_{13}N_3O_4$	61.73	4.21	13.50
				61.48	4.28	13.81
4d	67	141	$C_{16}H_{13}N_3O_4$	61.73	4.21	13.50
				61.66	4.32	13.45
5a	70	178	$C_{15}H_{10}N_2O_3S$	60.39	3.38	9.39
				60.65	3.61	9.03
5b	69	163	$C_{16}H_{11}N_3O_3$	65.62	3.78	14.33
				65.54	3.99	14.01
5c	62	168	$C_{16}H_{11}N_3O_3$	65.62	3.78	14.33
				65.30	3.61	14.30
5d	68	140	$C_{16}H_{11}N_3O_3$	65.62	3.78	14.33
				65.92	4.18	14.65

N-Nitroso-N-{4-[3-(2-thienyl)-2-propenoyl]phenyl}glycine (**4a**)

IR: 3200-2700 (OH), 1725 (CO), 1650 (CH=CH), 1600 (COO), 1450 (NO), 1040 (N-N). - ^{1}H-NMR: 4.85 (s, 2H, CH_2), 7.15-8.40 (m, 9H, CHCO, Ar-H, Ar-CH=).

Sydnone

1 mmole **4** was dissolved in 15 ml acetic anhydride and heated on a water bath for 2 h. The solvent was removed *in vacuo* and the residue was triturated with cold water and crystallized from methanol.

3-{4-[3-(3-pyridyl)-2-propenoyl]phenyl}sydnone (**5c**)

IR: 3110 (CH), 2940 (CH), 1760 (CO), 1725 (CO), 1670 (CH=CH). - ^{1}H-NMR: 7.60-8.65 (m, 11H, sydnone, CH=CH, Ar-H).

Microbiology

The microdilution susceptibility test in *Müller-Hinton* Broth (Oxoid) and *Sabouraud* Liquid Medium (Oxoid) was used for the determination of antibacterial and antifungal activity[12,13]. Test organisms: *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 as *Gram(-)* bacteria, *Streptococcus faecalis* ATCC 19433, *Staphylococcus aureus* ATCC 25923 as *Gram(+)* bacteria and *Candida albicans*, *Candida parapsilosis*, *Candida pseudotropicalis*, *Candida stellatoidea* as yeast like fungi.

Table 3: Antimicrobial activity of compounds **3** - **5**

Comp. No	MIC (µg/ml) A	B	C	D	E	F	G	H
3a	100	100	100	100	100	100	100	100
3b	100	100	100	100	200	100	100	100
3c	200	200	200	200	200	200	200	200
3d	100	50	100	100	100	100	100	100
4a	100	50	100	100	100	100	100	100
4b	50	50	50	50	25	25	25	25
4c	50	50	50	50	100	100	100	100
4d	100	100	100	100	100	100	100	100
5a	100	100	100	100	100	100	100	100
5b	50	50	50	50	100	100	100	100
5c	50	50	50	50	100	100	100	100
5d	50	50	50	50	50	50	50	50
Amp.	25	25	12.5	12.5	–	–	–	–
Clot.	–	–	–	–	25	12.5	12.5	12.5

A: *Escherichia coli*, B: *Pseudomonas aeruginosa*, C: *Streptococcus faecalis*, D: *Staphylococcus aureus*, E: *Candida albicans*, F: *C. parapsilosis*, G: *C. pseudotropicalis*, H: *C. stellatoidea*. MIC: Minimal inhibitory concentration. Amp.: Ampicilin trihydrate, Clot.: Clotrimazole.

The solution of compounds and ampicillin trihydrate and clotrimazole as controls were dissolved in DMSO at 1600 µg/ml. The twofold dilutions of the compounds were prepared (800, 400, ..., 6.25 µg/ml). The microorganism suspensitions at 10^6 CFU/ml (Colony Forming Unit/ml) concentration were inoculated to the corresponding wells. Plates were incubated at 36°C for 24 to 48 h. The incubation chamber was kept sufficiently humid. At the end of the incubation period the minimal inhibitory concentrations (MIC) were determined. Controls for the DMSO microorganisms and media microorganisms were also done.

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Verantwortlich für die Redaktion: Prof. Dr. W. Wiegrebe. Pharmazeutisches Institut der Universität Regensburg, Universitätsstraße 31, Postfach 397, D-93053 Regensburg. – Anzeigenleitung: R.J. Roth, D-69451 Weinheim –VCH Verlagsgesellschaft mbH (Geschäftsführer: Hans Dirk Köhler, Dr. Karlheinz Köpfer), Postfach 101161, D-69451 Weinheim – Alle Rechte, insbesondere die der Übersetzung in fremde Sprachen, vorbehalten. Kein Teil dieser Zeitschrift darf ohne schriftliche Genehmigung des Verlages in irgendeiner Form – durch Photokopie, Mikrofilm oder irgendein anderes Verfahren – reproduziert oder in eine von Maschinen, insbesondere von Datenverarbeitungsmaschinen verwendbare Sprache übertragen oder übersetzt werden. – All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without the permission in writing of the publishers. – Von einzelnen Beiträgen oder Teilen von ihnen dürfen nur einzelne Vervielfältigungsstücke für den persönlichen und sonstigen eigenen Gebrauch hergestellt werden. Die Weitergabe von Vervielfältigungen, gleichgültig zu welchem Zweck sie hergestellt werden, ist eine Urheberrechtsverletzung. Der Inhalt dieses Heftes wurde sorgfältig erarbeitet. Dennoch übernehmen Autoren, Herausgeber, Redaktion und Verlag für die Richtigkeit von Angaben, Hinweisen und Ratschlägen sowie für eventuelle Druckfehler keine Haftung. This journal was carefully produced in all its parts. Nevertheless, authors, editors and publishers do not warrant the information contained therein to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate. – Die Wiedergabe von Gebrauchsnamen, Handelsnamen, Warenbezeichnungen u. dgl. in dieser Zeitschrift berechtigt nicht zu der Annahme, daß solche Namen ohne weiteres von jedermann benutzt werden dürfen. Es handelt sich häufig um gesetzlich eingetragene Warenzeichen, auch wenn sie in dieser Zeitschrift nicht als solche gekennzeichnet sind. Texterfassung und EDV-Bearbeitung: Fa. Hellinger, D-69253 Heiligkreuzsteinach; Druck und Buchbinder: Rheinhessische Druckwerkstätte, D-55232 Alzey, – Unverlangt zur Rezension eingehende Bücher werden nicht zurückgesandt.

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