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Novel Analogues of Sydnone: Synthesis, Characterization and Antibacterial Evaluation

New sydnone derivatives bearing a substituted phenyl ring at the 3-position have been synthesized. Two separate series of 3-(carboxyphenyl)sydnone derivatives have been prepared by cyclization of the corresponding *N*-nitroso-*N*-(carboxyphenyl)-glycine **3**. The obtained 3-(carboxyphenyl)sydnones **4** were subjected to a series of different chemical reactions on the carboxylic acid group. Compound **5**, the potassium salt of **4a**, was reacted with α-chloroacetanilide derivatives **6** to give the corresponding esters **7**. On the other hand, the acid hydrazide **9** was condensed with different aromatic aldehydes to give the corresponding arylidene derivatives **10**. The synthesized compounds were tested for their antibacterial activities against both gram-positive and gram-negative organisms. Some of the test compounds exhibited high activity; among them, **10d** is considered to be a lead compound possessing high broad-spectrum antibacterial activity.

Keywords: Sydnone; Arylidenebenzoylhydrazine; Antibacterial agents

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Introduction

Combat against bacterial infections has resulted in the development of a wide variety of antibiotics. After years of misuse and overuse of antibiotics, bacteria are becoming antibiotic resistant, resulting in a potential global health crisis. There is already evidence that antibacterial resistance is associated with an increase in mortality. Frequently, it is recommended to use new antibacterial agents with enhanced broad-spectrum potency. Therefore, recent efforts have been directed toward exploring novel antibacterial agents. The potential biological activities of sydnones have received great interest; some sydnone derivatives possess antibacterial properties [1, 2]. We have recently described high antibacterial activities of some novel phenylsydnone derivatives having hydrazone, acid hydrazide and arylidenehydrazine counterparts at the 4-position of the phenyl ring [3]. In continuation of our interest in chemistry and biological properties of sydnone derivatives, we herein report preparative methods for various derivatives of the sydnone ring system as well as their antibacterial properties. The antibacterial activities of many compounds carrying amide and ester moieties were reported [4–7]. Accordingly, conjugation of both ester and arylamide moieties to produce carbamoylmethoxycabonyl derivatives was achieved. Furthermore, we deemed it interesting to study the influence of further concomitant substitutions such as acidhydrazide and arylidenehydrazinocarbonyl on the 3-position of the phenyl ring. On the basis of these considerations we have planned the preparation of a new series of 3-phenylsydnone bearing different substitution at the 3- or 4-position of the phenyl ring in order to further explore the biological properties of these compounds.

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Results and discussion

Chemistry

The sydnone derivatives were prepared as shown in Schemes 1 and 2. Baker et al. [8–10] have reported a standard procedure for preparation of sydnones. The conventional synthesis of 3-arylsydnone derivatives involves reaction of equimolar amounts of 4-aminobenzoic acid (**1a**) with a neutralized solution of chloroacetic acid to yield the *N*-(4-carboxyphenyl)glycine (**2a**) (Scheme 1). As candidate for cyclization, *N*-nitroso-*N*-(4-carboxyphenyl)glycine (**3a**) was used, which in turn was prepared through nitrosation of **2a** with nitrous acid. One of the major and most convenient routes for sydnone ring formation is cyclodehydration of **3a** through refluxing with acetic anhydride to yield 3-(4-carboxyphenyl)sydnone (**4a**) [11, 12]. The high reactivity (Schemes 1 and 2) of the potassium salts of carboxylic acids with alkyl halides was reflected in the reactivity of the potassium salt of 3-(4-carboxyphenyl)sydnone (**5**) (Scheme 1). Thus, treatment of **5** with variously substituted α-chloroacetan-

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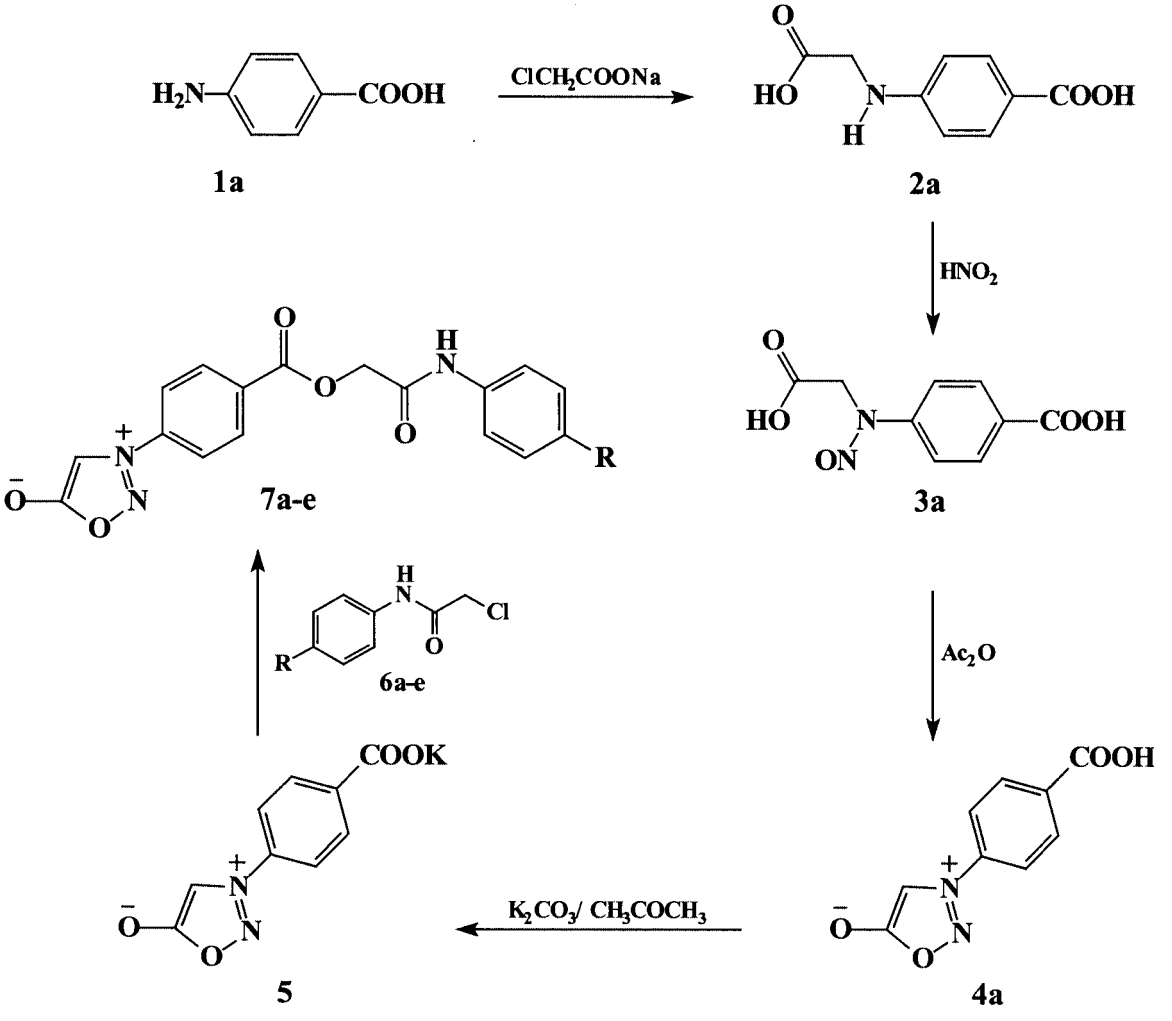
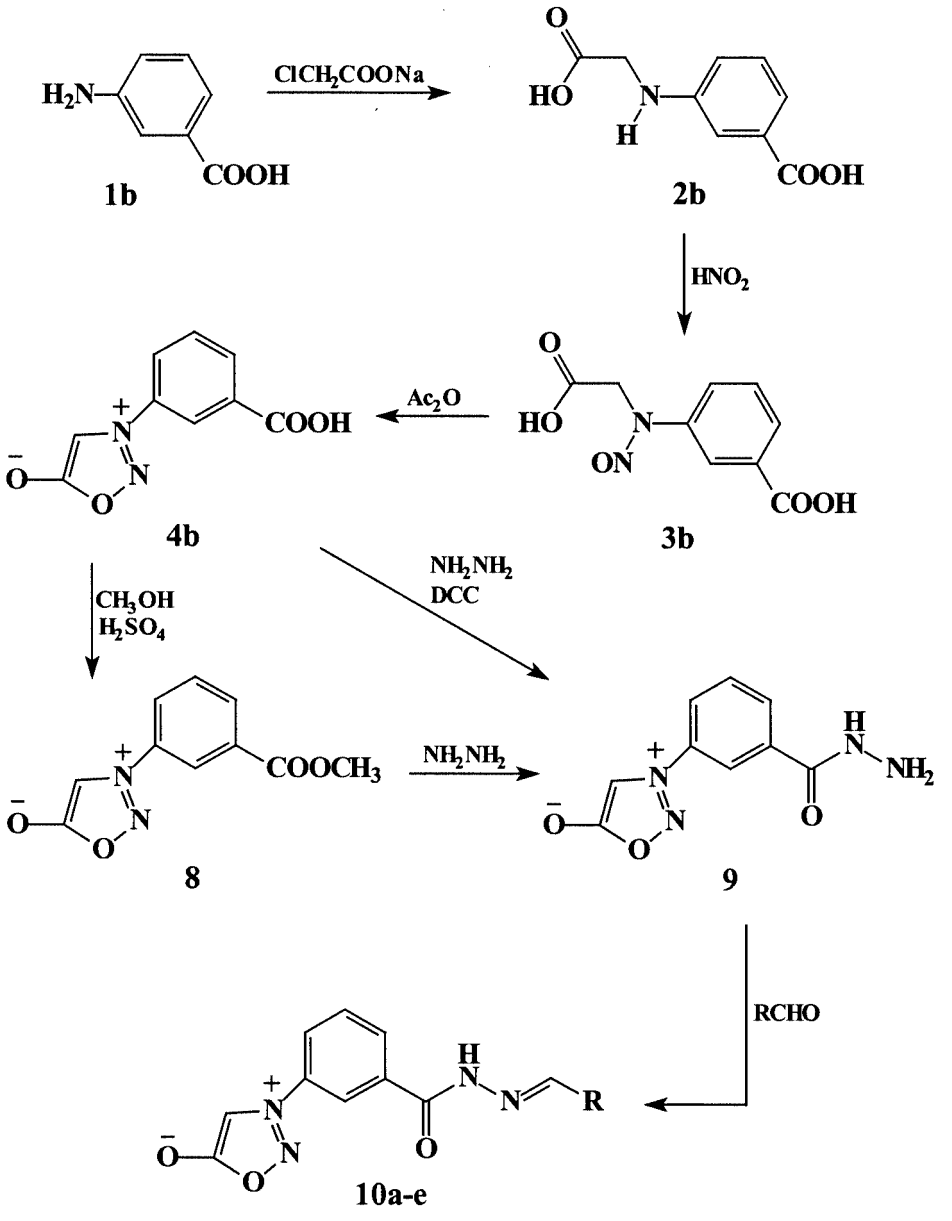


Scheme 1.

ilides **6** resulted in the formation of the corresponding esters **7**. Moreover, it was reported that esters of carboxylic acids were prepared in high yields from their sodium salts through reaction with primary and secondary alkyl bromides and iodides at room temperature in dipolar aprotic solvents, especially hexamethylphosphoric triamide (HMPT) [13]. In the current work, potassium salt was chosen over sodium salt due to the higher reactivity of potassium. In turn, the potassium salt was prepared by a salting-out process, using a mild basic aqueous potassium carbonate solution and acetone at room temperature. Potassium carbonate was used to avoid the possibility of alkaline hydrolysis of the sydnone ring with the strong basic potassium hydroxide. Compounds **7** were prepared by heating a mixture of the appropriate α-chloroacetanilide **6** and potassium 4-(ψ-5-oxo-1,2,3-oxadiazol-3-yl)-phenyl carboxylate **5** in the presence of DMF as a solvent (Scheme 1). By an analogous sequence of steps, 3-(3-carboxyphenyl)sydnone (**4b**) was prepared, starting with 3-aminobenzoic acid (**1b**) and applying the same general approach (Scheme 2). However, after sydnone ring formation, the resulting carboxylic acid **4b** can be converted into various functionalities. The acid hydrazide **9** can be obtained through two different procedures. Compound **9** could be directly synthesized from the acid **4b** by stirring at room temperature with hydrazine in the presence of dicyclohexylcarbodiimide (DCC). The analogous reaction between the acid **4b** and methanol in the presence of sulfuric acid at



Scheme 2.

room temperature afforded the formation of the corresponding ester 3-(3-methoxycarbonylphenyl)sydnone (**8**). However, the acid hydrazide **9** was advantageously prepared by adoption of the ester functional group transformation process. Thus, refluxing ester **8** with hydrazine in the presence of ethanol resulted in the formation of 3-(3-hydrazinocarbonylphenyl)sydnone (**9**). Compound **9** was used as a precursor for the synthesis of a series of hydrazone derivatives **10** by refluxing with the appropriate aromatic aldehyde in ethanol (Scheme 2). See Table 1 for a summary of the physicochemical data of the newly synthesized compounds.

Antibacterial screening

All sydnone derivatives synthesized were tested *in vitro* for their antibacterial activities. Three groups of 3-

Table 1. Physicochemical data of the new compounds.

Comp.	R	MP (°C)	Yield (%)	Mol. Form.
7a	H	197–199	80	$C_{17}H_{13}N_3O_5$
7b	$COOC_2H_5$	85–87	58	$C_{20}H_{17}N_3O_7$
7c	COOH	255–257	68	$C_{18}H_{13}N_3O_7$
7d	$COCH_3$	187–189	78	$C_{19}H_{15}N_3O_6$
7e	OC_2H_5	193–195	75	$C_{19}H_{17}N_3O_6$
10a	C_6H_5	278–280	73	$C_{16}H_{12}N_4O_3$
10b	4-Cl-C_6H_4	>300	85	$C_{16}H_{11}ClN_4O_3$
10c	4-NO_2-C_6H_4	>300	80	$C_{16}H_{11}N_5O_5$
10d	2-Cl-5-NO_2-C_6H_3	>300	75	$C_{16}H_{10}ClN_5O_5$
10e	2-Furyl	258–260	65	$C_{14}H_{10}N_4O_4$

phenylsydnone were selected for biological screening. Group classification depends on the nature of the acid derivative existing on the phenyl ring. The first group consists of 3-phenylsydnones bearing free carboxylic acid group **4** or its simple derivatives such as simple alkyl ester **8** or acid hydrazide **9**. The second group **7** possesses bulky esters of variously substituted acetanilide derivatives. The last group bears arylidenehydrazinocarbonyl functionality at the phenyl ring **10**. The test compounds were screened against four strains of pathogenic microorganisms, two gram-positive and two gram-negative organisms, using ciprofloxacin as a reference standard. The minimum inhibitory concentrations (MICs, μg/mL) were determined using the standard agar dilution method [14]. MIC values are summarized in Table 2. From the compiled data, it would be obvious that the novel sydnone derivatives are especially potent against gram-positive organisms, particularly against the *Bacillus subtilis* strain. Regarding the first group of tested sydnones, it seems that all members show almost comparable activities. However, compound **9**, with acid hydrazide functionality, is the most active, especially against gram-positive organisms.

Moreover, variation of the position of the carboxylic group from position 4 as in **4a** to position 3 as in **4b**

Table 2. *In vitro* antibacterial activities of the new compounds.

Comp.	Minimum Inhibitory Concentrations (MIC)[§] (μg/mL)			
	Gram-positive Organisms[b]		Gram-negative Organisms[‡]	
	B. su.	*S. au.*	*E. co.*	*P. ae.*
4a	16	32	64	32
4b	16	16	64	64
7a	4	4	4	8
7b	32	32	64	32
7c	8	16	16	8
7d	16	32	32	64
7e	32	64	64	64
8	8	16	32	64
9	8	8	32	32
10a	32	64	> 128	64
10b	2	4	4	4
10c	8	16	8	16
10d	1	1	0.25	0.125
10e	64	64	>128	64
Ciprofloxacin	0.5	1	0.064	0.032

§ MIC is the lowest concentration of compound needed for prevention of visible growth of microorganisms, reported as the average value of duplicate determinations. MIC values were obtained by the use of an agar dilution method, whereby organisms were deposited onto medicated agar plates by the replication device of Steers et al. [14].

‡ Organisms selected: *B. su., Bacillus subtilis* ATCC 6633; *S. au.*, *Staphylococcus aureus* ATCC 29213; *E. co., Escherichia coli* ATCC 25922; *P. ae., Pseduomonas aeruginosa* ATCIC 9027.

revealed that this change has no significant effect on the antibacterial activity. We have briefly investigated the structure-activity relationship of the arylhydrazone group in compounds **10**. The presence and lipophilicity of substituents at the arylidene phenyl ring were considered to be a key factor in determining biological activity. In particular, it was found that the coupled presence of a chloro group at the 2-position and a nitro group at the 5-position in compound **10d** is highly effective for enhancing the antibacterial activity, particularly against gram-negative bacteria. However, compound **10b** exhibited better activity than compound **10c** against all types of organisms. This could be reasonably attributed to the presence of the chloro group, which is more lipophilic than the nitro group of **10c**. At this point, it is necessary to mention the importance of the substituents at the phenyl ring with respect to biological activity. In order to define more clearly the role of the substituents for the activity profile, we have prepared the unsubstituted phenyl derivative **10a** in addition to the unsubstituted furyl analogue **10e**. When directly compared to the substituted analogues in this study, compounds **10a** and **10e** exhibited decreased antibacterial activity against all organisms. However, these results run contrary to the activity profile of the esters **7**, in which case the ethyl ester-containing compound at the terminal phenyl ring, exemplified by compound **7b**, was found to be less potent than the free carboxylic acid-containing compound, such as **7c**. Moreover, the lipophilic methylcarbonyl group in compound **7d** revealed lower biological activity than the parent carboxylic acid **7c**. However, compound **7a** with an unsubstituted phenyl ring possesses the highest activity among the members of this series of compounds.

In conclusion, the results of the present study indicate that 3-arylsydnones possess antibacterial properties, and substitutions at the 3-phenyl ring might be detrimental with regard to activity. Substituent combination at the terminal phenyl ring of arylidene derivatives of acid hdrazide might produce powerful antibacterial agents. Therefore, derivative **10d** with its potent broadened spectrum of antibacterial activity is an interesting lead compound for further development.

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Experimental

Chemistry

Melting points (°C, uncorrected) were determined on a Fischer-Johns apparatus. IR spectra (KBr) were recorded on a Pye-Unicam SP1000 Spectrometer (ν in cm^{-1}). ^{1}H- and ^{13}C-NMR spectra were recorded on a FT-NMR spectrometer (400 MHz) JNM-LA, using TMS as internal standard (chemical shifts in ppm, δ units). Mass spectral data were recorded on a JEOL JMS-600H spectrometer. The results of elemental analyses (C, H, N) were within $\pm$ 0.4% of the theoretical values. Thin layer chromatography was performed on silica gel GLF plates, 250 microns. The compound 3-(4-carboxy-phenyl)sydnone (**4a**) was prepared according to published procedure [15]. The intermediates **6a–f** were prepared applying reported methods [16–20].

*N-(3-Carboxyphenyl)glycine (**2b**)*

A solution of chloroacetic acid (9.45 g, 0.1 mol) in water (100 mL) was neutralized with a 10% sodium hydroxide solution while cooling. 3-Aminobenzoic acid (**1b**) (13.8 g, 0.1 mol) was added to the product, and the reaction mixture was refluxed for 10 h. After cooling to room temperature, the separated solid was collected by filtration, dried and recrystallized from ethanol to give 16.8 g (85%) of **2b**, m.p. 260–262°C. ^{1}H-NMR (DMSO-d_6): 4.73 (s, 2H, CH_2), 5.93 (br s, 1H, NH; D_2O exchangeable), 7.41–8.23 (m, 4H, Ar-H), 12.11 (br s, 2H, 2COOH; D_2O exchangeable).

*N-Nitroso-N-(3-carboxyphenyl)glycine (**3b**)*

To a well-stirred mixture of the glycine derivative **2b** (1.95 g, 10 mmol) in 10% hydrochloric acid (10 mL) at 0–5°C, a solution of sodium nitrite (0.69 g, 10 mmol) in water (10 mL) was added dropwise over a period of 30 min. Stirring was continued for a further 1 h. The product was collected by filtration, washed thoroughly with cold water, dried and recrystallized from methanol to yield 1.64 g (73%) of **3b**, m.p. 158–160°C. IR: 3240 (OH), 1712 (C=O), 1569 (N=O).

*3-(3-Carboxyphenyl)sydnone (**4b**)*

A mixture of *N*-nitrosoglycine derivative **3b** (2.9 g, 13 mmol) and acetic anhydride (15 mL) was heated in a water bath for 3 h. Excess solvent was removed under reduced pressure, and the residue was triturated with cold water and recrystallized from methanol to give 1.99 g (80%) of **4b**, m.p. 245–247°C. IR: 3138 (CH, sydnone), 1736 (C=O, sydnone), 1702 (C=O). ^{1}H-NMR (DMSO-d_6): 7.63–8.55 (m, 5H, Ar-H and CH sydnone), 11.30 (s, 1H, COOH; D_2O exchangeable).

*Potassium 4-(ψ-5-oxo-1,2,3-oxadiazol-3-yl)phenyl carboxylate (**5**)*

3-(4-Carboxy-phenyl)sydnone (**4a**) (2 g, 10 mmol) was dissolved in a 20% potassium carbonate solution (8 mL) at room temperature. The aqueous solution thus obtained was filtered, and the filtrate was slowly added to ice-cold acetone. The pale orange crystals obtained were collected by filtration, washed with anhydrous acetone and then air dried to give the potassium salt (2.32 g, 95%) of **5**, m.p. >300°C. ^{1}H-NMR (DMSO-d_6): 7.31–8.42 (m, 5H, Ar-H and CH sydnone).

*3-[4-(Arylcarbamoylmethoxycarbonyl)phenyl]sydnones (**7a**–**e**)*

A mixture of the potassium salt of 3-(4-carboxyphenyl)sydnone (**5**) (2.93 g, 12 mmol) and the appropriate substituted chloroacetanilide **6a**–**e** (10 mmol) in DMF (20 mL) was heated in a water bath for 5 h, allowed to cool to room temperature and then poured over ice-water. The separated solid was collected by filtration, dried and recrystallized from DMF/water to give pure products. IR: **7a**: 3268 (NH), 3195 (CH, sydnone), 1739 (C=O, sydnone), 1720 (C=O, ester), 1692 (C=O, amide). **7b**: 3275 (NH), 3178 (CH, sydnone), 1741 (C=O, sydnone), 1722, 1707 (two C=O, ester), 1698 (C=O, amide). **7c**: 3400 (OH), 3268 (NH), 3195 (CH, sydnone), 1739 (C=O, sydnone), 1720 (C=O, ester), 1692 (C=O, amide). **7d**: 3250 (NH), 3132 (CH, sydnone), 1770 (C=O, sydnone), 1745 (C=O, ester), 1732 (C=O, $COCH_3$), 1662 (C=O, amide). **7e**: 3286 (NH), 3120 (CH, sydnone), 1760 (C=O, sydnone), 1730 (C=O, ester), 1684 (C=O, amide). ^{1}H-NMR (DMSO-d_6), **7b**: 1.31 (t, 3H, CH_3), 4.28 (q, 2H, CH_2), 5.04 (s, 2H, CH_2), 7.70–8.33 (m, 9H, Ar-H and C-H sydnone), 10.67 (s, 1H, NH; D_2O exchangeable). **7e**: 1.32 (t, 3H, CH_3), 3.99 (q, 2H, CH_2), 4.98 (s, 2H, CH_2), 6.88–8.35 (m, 8H, Ar-H), 7.94 (s, 1H, C-H sydnone), 10.13 (s, 1H, NH; D_2O exchangeable). MS (m/z), **7a**: 281 $C_{16}H_{13}N_2O_3$ (M-58, 100), 162 $C_9H_8NO_2$ (15.1), 148 $C_8H_6NO_2$ (14.5), 104 C_7H_6N (42.3).

*3-(3-Methoxycarbonylphenyl)sydnone (**8**)*

A mixture of 3-(3-carboxyphenyl)-sydnone (**4b**) (2.1 g, 10 mmol), absolute methanol (50 mL) and concentrated sulfuric acid (1 mL) was stirred at room temperature for 24 h. Then a solution of sodium bicarbonate (5%) was added portionwise until effervescence ceased. The solid obtained was collected by filtration, suspended in sodium bicarbonate solution (5%, 20 mL) and stirred for 10 min to dissolve unreacted acid. The precipitate was collected by filtration, washed with water, dried and recrystallized from ethanol to give 1.76 g (80%) of **8**, m.p. 178–180 °C. IR: 3114 (CH, sydnone), 1768 (C=O, sydnone), 1725 (C=O). ^{1}H-NMR (DMSO-d_6): 3.82 (s, 3H, CH_3), 7.38-8.47 (m, 5H, Ar-H and CH sydnone).

*3-[3-(Hydrazinocarbonyl)phenyl]sydnone (**9**)*

Method 1: A mixture of 3-(3-methoxycarbonylphenyl)sydnone (**8**) (2.2 g, 10 mmol) and hydrazine hydrate 99% (1 g, 32 mmol) in ethanol (20 mL) was heated under reflux for 3 h. The formed precipitate was collected by filtration, washed with boiling ethanol and recrystallized from methylene chloride/*n*-hexane to give 1.87 g (85%) of **9**, m.p. 268–270 °C. IR: 3320, 3280 (NH, NH_2), 3098 (CH, sydnone), 1752 (C=O, sydnone), 1720 (C=O). ^{1}H-NMR (DMSO-d_6): 5.32 (br s, 2H, NH_2; D_2O exchangeable), 7.51–8.60 (m, 5H, Ar-H and CH sydnone), 10.61 (br s, 1H, NH; D_2O exchangeable).
Method 2: To a stirred solution of 3-(3-carboxyphenyl)sydnone (**4b**) (2.06 g, 10 mmol) in THF (30 mL) was added dicyclohexylcarbodiimide (DCC) (2.06 g, 10 mmol), followed by hydrazine hydrate 99% (5 mL). After stirring for 24 h at room temperature, the reaction mixture was filtered and the filtrate was evaporated *in vacuo*. The solid obtained was recrystallized from methylene chloride/*n*-hexane to give 1.3 g (60%) of **9**, m.p. 269–271 °C.

*2-Arylidene-1-[3-(ψ-5-oxo-1,2,3-oxadiazol-3-yl)benzoyl]-hydrazines (**10a**–**e**)*

A mixture of 3-(3-hydrazinocarbonylphenyl)sydnone (**9**) (2.36 g, 10 mmol) and the appropriate aromatic aldehyde (10 mmol) in absolute ethanol (25 mL) was refluxed for 5 h and then cooled to room temperature. The separated solid was collected by filtration, dried and recrystallized from DMF to give pure product. IR, **10a**: 3300 (NH), 3136 (CH, sydnone), 1733 (C=O, sydnone), 1674 (C=O, amide), 1595 (C=N-). **10b**: 3286 (NH), 3179 (CH, sydnone), 1757 (C=O, sydnone), 1666 (C=O, amide), 1587 (C=N-). **10c**: 3279 (NH), 3117 (CH, sydnone), 1735 (C=O, sydnone), 1670 (C=O, amide), 1584 (C=N-). **10d**: 3255 (NH), 3115 (CH, sydnone), 1732 (C=O, sydnone), 1672 (C=O, amide), 1600 (C=N-). **10e**: 3262 (NH), 3130 (CH, sydnone), 1750 (C=O, sydnone), 1660 (C=O, amide), 1622 (C=N-). ^{1}H-NMR (DMSO-d_6), **10a**: 7.52–8.47 (m, 10H, Ar-H, N=C-H, and C-H sydnone), 12.16 (s, 1H, NH; D_2O exchangeable). **10d**: 7.86–8.90 (m, 9H, Ar-H, N=C-H, and C-H sydnone), 12.52 (s, 1H, NH; D_2O exchangeable). MS (m/z), **10c**: 323 $C_{16}H_{11}N_4O_4$ (M-30, 12.7), 295 $C_{15}H_{11}N_4O_3$ (M-58, 100), 221 $C_{14}H_9N_2O$ (6.7), 132 $C_7H_4N_2O$ (8.7).

Antibacterial activity

The synthesized compounds were evaluated for their *in vitro* antibacterial activity against representative gram-positive and gram-negative organisms applying the standard agar dilution method using Mueller-Hinton medium. MIC were determined after 18 h of incubation at 35 °C. The concentrations of the bacterial suspensions were verified by determining standard colony counts on antibiotic-free agar plates. MIC was considered to be the lowest concentration that completely inhibited growth on agar plates, disregarding a single colony or a faint haze caused by the inoculum. Ciprofloxacin was used as a reference compound.

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