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Synthesis and Biological Testing of Novel Analogues of Sydnone as Potential Antibacterial Agents

Several series of 3-phenylsydnone derivatives conjugated to well-known moieties with antibacterial activity were synthesized via several routes. These derivatives include 3-cyano-2-oxopyridine, 2-amino-3-cyanopyridine, 2-arylidene-1-ethylidenehydrazine and 2-aroyl-1-ethylidenehydrazine moieties. Thus, the key intermediate 3-(4-acetylphenyl)sydnone (**3**) was allowed to react with the appropriate aldehyde, ethyl cyanoacetate or malononitrile in presence of excess ammonium acetate in two steps (method 1) or through a one-pot reaction technique (methods 2 and 3) to give the corresponding sydnone derivatives **5** and **6**, respectively. Moreover, condensation of compound **3** with hydrazine hydrate followed by the reaction with the appropriate aldehyde, mono- and dicarboxylic acid hydrazide yielded the corresponding sydnone derivatives **8**, **9** and **10**, respectively. Most of the synthesized compounds were screened for their in vitro antibacterial activity against various pathogenic organisms of both Gram-positive and Gram-negative bacteria. The minimum inhibitory concentrations (MICs) were determined using agar dilution method.

Keywords: Sydnone; Cyanooxopyridine; Aminocyanopyridine; Arylidenehydrazine; Aroylhydrazine; Antibacterial agents

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Introduction

Research on the field of antimicrobial agents is of significant interest in the scope of medicinal chemistry aiming for the discovery of new agents having potential activity, broader spectrum, less toxicity, and safer therapeutic profiles than the currently available ones. The primary aim was to synthesize different sydnones conjugated with effective and well-known pharmacophoric moieties of potential antibacterial activity, as for example, cyanooxopyridine, aminocyanopyridine and substituted hydrazine moieties. Several publications have pointed out the value of sydnones as antimicrobial agents [1–5], as compounds I–IV (Figure 1). It was observed that in the majority of the reported compounds, the presence of substituted phenyl group at the 3-position of the sydnone was a common structural feature. On the other hand, the antimicrobial activity of pyridine ring substituted with a wide variety of functionalities was reported [6–8]. Cyanooxopyridines and aminocyanopyridines were among pyridine derivatives that show significant activity [9, 10]. In addition, earlier reports revealed that several hydrazones e.g., verazide V, ftivazide VI and others, exhibit antibacterial activity [11, 2]. The biological activity associated with these compounds was attributed to the presence of the (–CONH–N=CH–) moiety. Likewise, several hydrazine derivatives especially 2-arylidene and 2-aroylhydrazines were reported to possess good antibacterial activity, e.g. isonicotinyl hydrazones [13] and compounds with the general structure **VII** [14] (Figure 1). Taking the above mentioned considerations into account, molecular conjugation of the sydnone moiety with two or more active counterparts was designed and synthesized with the hope of producing novel sydnone derivatives that possess good antibacterial activity.

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Results and discussion

Chemistry

The synthetic strategies adopted to obtain the target compounds are summarized in Schemes 1-3. The standard procedure that was reported earlier [15, 16] and later by Baker et al. [17–19] was adopted for the preparation of the compound 3-(4-acetylphenyl)sydnone (**3**) (Scheme 1). Reaction of equimolar amounts of 4-aminoacetophenone with aqueous solution of sodium salt of chloroacetic acid yielded *N*-(4-acetylphenyl)glycine (**1**), which was nitrosated by the action of sodium nitrite in dilute hydrochloric acid solution to

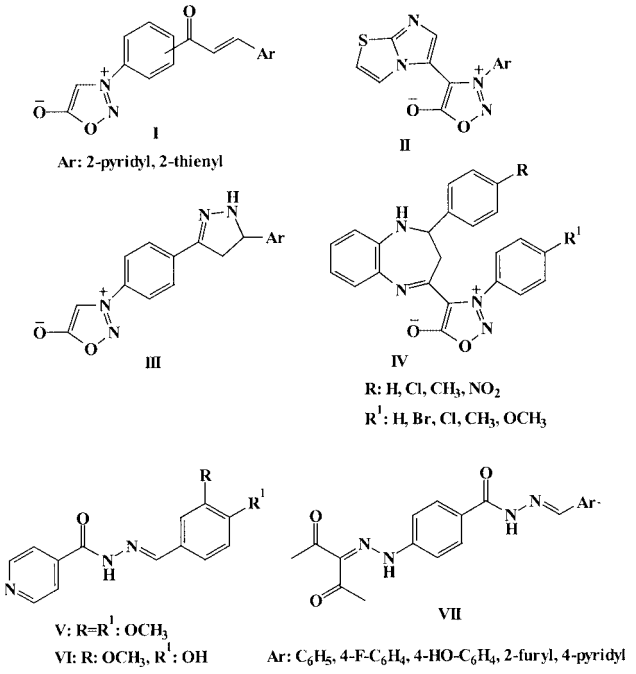
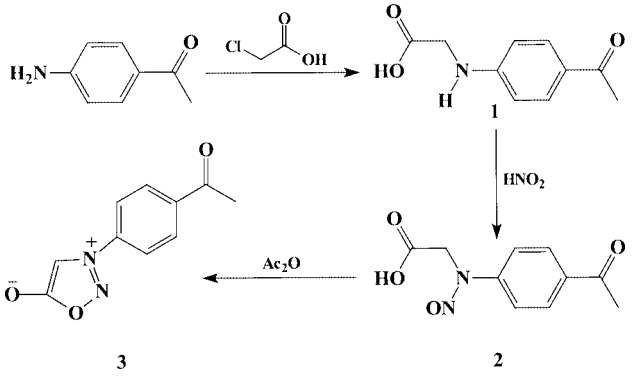


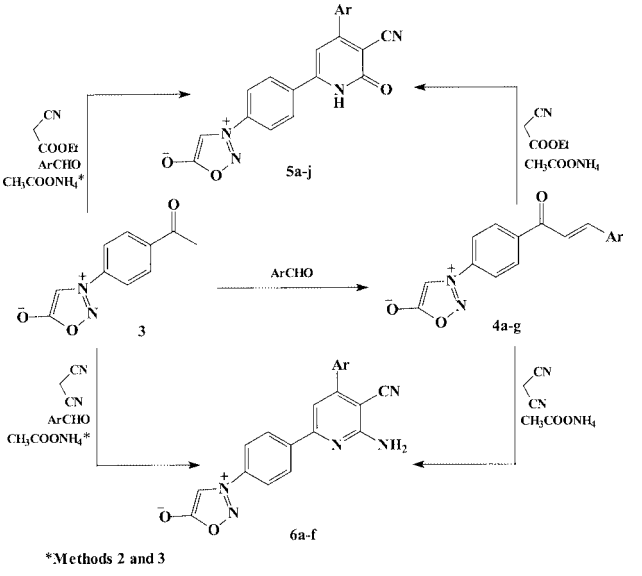
Figure 1. Representative examples of sydnones and hydrazine derivatives of antimicrobial acitivities.



Scheme 1.

give the *N*-nitroso-*N*-(4-acetylphenyl)glycine (**2**). The *N*-substituted *N*-nitrosoglycines were reported to be cyclized to the corresponding sydnones by the action of trifluoroacetic anhydride in dichloromethane at room temperature [18], or by heating in acetic anhydride [20, 21]. Compound **2** was successfully cyclized to its sydnone analogue **3** in a 75% yield by the action of acetic anhydride (Scheme1) [3]. Compound **3** was considered an important synthon for the construction of the pyridine ring. 3-[4-(4-Aryl-3-cyano-1,2-dihydro-2-oxo-6-pyridyl)phenyl]sydnones **5a**–**j** were synthesized following the two strategies illustrated in Scheme 2. The first one was applied through the formation of the intermediates 3-[4-(3-aryl-1-oxo-2-propen-1-yl)phenyl-]sydnones **4a**–**g** via Claisen-Schmidt condensation of 3-(4-acetylphenyl)sydnone (**3**), which was subsequently allowed to react with the appropriate aromatic aldehyde in alcoholic sodium hydroxide (method 1) [3, 22]. Moreover, it was reported that cyanooxopyridines were synthesized in a one-pot reaction by heating compound **3** with the aldehydes in presence of ammonium acetate neat [23] or in a suitable solvent [24-26]. In the present work, compounds **5a**–**j** were synthesized by condensation of compound **3** with the appropriate aromatic aldehyde and ethyl cyanoacetate in presence of excess ammonium acetate using ethanol as solvent through a one-pot reaction (method 2) or by heating the previous reaction mixture neat in an oil bath at 140-160°C (method 3). All members of the series **5a**–**j** were prepared by the 3 methods except compounds **5c**, **5e** and **5i** which were prepared by methods 2 and 3 only. Comparison of the yield data of the 3 methods revealed that the one-pot reaction methods were the best in terms of yield percentage especially when the reaction was carried out neat (method 3) (Table 1).

Construction of an aminocyanopyridine ring could be achieved by similar methods [27–30] applied for the synthesis of cyanooxopyridines except using malononitrile instead of ethyl cyanoacetate. Thus, sydnone analogues **6a**–**f** were synthesized by the reaction of compounds **4a**–**g**, malononitrile and ammonium acetate in ethanol or *n*-butanol as solvents (method 1). They had been also synthesized by condensation of



Scheme 2.

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Table 1. Physicochemical data of the new compounds.

Comp.	Ar	MP (°C)	Solvents†	Yield (%) A/B/C‡	Mol. Formula
5a	C_6H_5	268–270	EA	17/23/30	$C_{20}H_{12}N_4O_3$
5b	2-Br-C_6H_4	256–257	EA	30/40/47	$C_{20}H_{11}BrN_4O_3$
5c	2-Cl-C_6H_4	280–282	DW	–/25/34	$C_{20}H_{11}ClN_4O_3$
5d	4-Cl-C_6H_4	273–275	DW	28/34/38	$C_{20}H_{11}ClN_4O_3$
5e	4-$(CH_3)_2N$-C_6H_4	160–162	EA	–/18/23	$C_{22}H_{17}N_5O_3$
5f	4-HO-C_6H_4	178–180	EA	20/23/30	$C_{20}H_{12}N_4O_4$
5g	4-H_3CO-C_6H_4	252–254	EA	20/26/35	$C_{21}H_{14}N_4O_4$
5h	4-NO_2-C_6H_4	>300	DW	35/43/50	$C_{20}H_{11}N_5O_5$
5i	2-Cl-5-NO_2-C_6H_3	191–193	EE	–/29/30	$C_{20}H_{10}ClN_5O_5$
5j	2-Furyl	>300	DT	19/20/25	$C_{18}H_{10}N_4O_4$
6a	C_6H_5	193–195	EA	10/22/15	$C_{20}H_{13}N_5O_2$
6b	2-Br-C_6H_4	205–207	DW	–/15/12	$C_{20}H_{12}BrN_5O_2$
6c	4-Br-C_6H_4	187–189	EA	–/30/30	$C_{20}H_{12}BrN_5O_2$
6d	4-Cl-C_6H_4	239–241	DW	20/24/24	$C_{20}H_{12}ClN_5O_2$
6e	4-H_3CO-C_6H_4	263–265	DW	15/20/17	$C_{21}H_{15}N_5O_3$
6f	4-NO_2-C_6H_4	246–248	DW	–/14/11	$C_{20}H_{12}N_6O_4$
8a	C_6H_5	173–175	E	74	$C_{17}H_{14}N_4O_2$
8b	4-Br-C_6H_4	184–185	EA	55	$C_{17}H_{13}BrN_4O_2$
8c	4-Cl-C_6H_4	189–190	E	67	$C_{17}H_{13}ClN_4O_2$
8d	4-HO-C_6H_4	196–197	ED	55	$C_{17}H_{14}N_4O_3$
8e	4-NO_2-C_6H_4	192–193	ED	72	$C_{17}H_{13}N_5O_4$
8f	2-Cl-5-NO_2-C_6H_3	135–236	ED	60	$C_{17}H_{12}ClN_5O_{24}$
8g	2,6-Cl_2-C_6H_3	186–188	E	83	$C_{17}H_{12}Cl_2N_4O_2$
8h	2-Furyl	167–168	EA	42	$C_{15}H_{12}N_4O_3$
9a	C_6H_5	225–227	DW	73	$C_{17}H_{14}N_4O_4$
9b	4-HO-C_6H_4	258–260	DW	60	$C_{17}H_{14}N_4O_4$
9c	4-Pyridyl	234–236	DW	68	$C_{16}H_{13}N_5O_3$
9d	2-Furyl	205–207	DW	70	$C_{15}H_{12}N_4O_4$
10	–	210–212	DW	65	$C_{23}H_{20}N_8O_6$

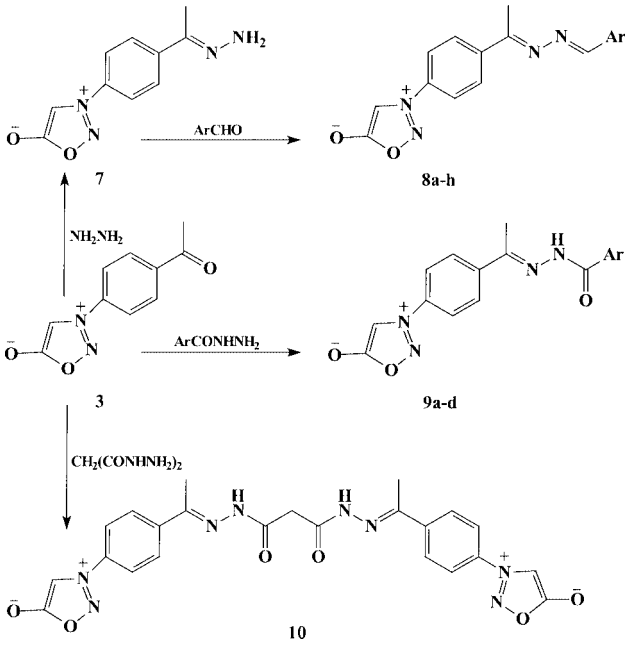
† Solvents: DT: DMF/toluene; DW: DMF/water; E: ethanol; EA: ethanol/acetone; ED: ethanol/ DMF; EE: ethanol/ ethyl acetate.

‡ A: method 1, B: method 2, C: method 3.

compound **3** malononitrile and the appropriate aldehyde in the presence of ammonium acetate using ethanol as a solvent (method 2) or neat in an oil bath at 140–160 °C (method 3) through a one-pot reaction technique (Scheme 2). All the synthesized compounds belonging to the series **6a–j** were prepared by the 3 methods except compounds **6b**, **6c** and **6f** were prepared by methods 2 and 3 only. Comparison of the yield data of the 3 methods showed that there was no significant difference between them. On the other hand, compound **3** was used as a precursor for the synthesis of other target compounds **7–10**. Compounds **8a–h** were prepared by stirring at room temperature for 8 h or refluxing for 1 h a mixture of 3-(4-acetylphenyl)sydnone (**3**) and hydrazine hydrate in presence of ethanol as a solvent to yield compound **7** in a high yield. Condensation of the latter with the appropriate aldehyde in ethanol gave the target compounds **8a-h**. Interaction of compound **3** with the appropriate mono- and dicarboxylic acid hydrazide yielded the corresponding sydnone derivatives **9a–d** and **10**, respectively (Scheme 3).

Antibacterial Screening

We carried out the screening experiments in vitro for antibacterial activities of the sydnone analogues. Four



Scheme 3.

groups of sydnone were subjected to biological testing. The first group comprises 3-phenylsydnone derivatives with the phenyl ring bearing a pyridine nucleus at the 4-position **5** and **6**. The second structural feature is represented by **7** with the 3-phenyl ring substituted at the 4-position with a hydrazone residue. The remaining two groups have the *N*-2 of **7** substituted with either arylidene group **8** or aroyl functionality **9**. To substantiate our antibacterial results, we screened these compounds against an assortment of two Gram-positive and two Gram-negative organisms using ciprofloxacin as a reference standard. The minimum inhibitory concentrations (MICs, μg/mL) were determined using standard agar dilution method [31]. The MIC values are summarized in Table 2. From the obtained data, it is clear that all the tested members of the pyridine series **5** and **6** possess higher activity than the parent acetyl derivative **3**. Among the pyridine series, the lipophilic bromophenyl ring in compound **5b** showed high activity against both types of bacteria, particularly, the Gram-negative organisms. On the other hand, the less lipophilic hydroxyphenyl group of **5f** revealed low activity while **5h** with a nitrophenyl residue possesses good activity. However, the order of activity observed with the 2-oxopyridine derivatives of sydnone **5** was also explored with the 2-aminopyridine series **6**. It was found that compound **6c** with bromophenyl counterpart is the most active member of this series against both Gram-positive and Gram-negative organisms and it is among the most active compounds tested. However, compound **6a** with an unsubstituted phenyl ring was the least active of this group of compounds. Alternatively, a nitrophenyl nucleus in place of the phenyl ring gave compound **6f** with better activity against Gram-positive than Gram-negative organisms. On the contrary, compound **7** manifested low antibacterial activity. On the other hand, substitution of the *N*-2 of **7** with arylidene moieties gave compounds **8**. Among this series of compounds, compound **8b** with a bromophenyl ring possessed the highest activities against all types of microorganisms. Against *B. subtilis*, **8b** showed activity almost equal to that of the standard ciprofloxacin. Compound **8h** with a furyl group comes at the second rank in activity against *B. subtilis*. Moreover, compound **8c** with a chlorophenyl moiety, is among the most active members of the test compounds. Compounds **9** with an aroyl group on the *N*-2 of compound **7** have moderate antibacterial activity with compound **9c** being the least active. In summary, compounds **8b**, **6c** and **5b**, having the common structural feature of a bromophenyl moiety, exhibit the highest antibacterial activities.

In conclusion, the results of the present study indicate that sydnone derivatives containing pyridine nucleus possess high antibacterial activity when a bromophenyl group is incorporated into the pyridine nucleus. On the other hand, replacement of the pyridine nucleus with an unsubstituted hydrazone residue resulted in formation of compound **7** with modest antibacterial activity. However, substitution at the *N*-2 of the hydrazine portion with an arylidene counterpart bearing a bromo group resulted in compound **8b** with the highest potency and a broadened spectrum of antibacterial activity in vitro. In addition, compounds **8c** with a chlorobenzylidene portion and **8h** with a furylmethylidene group as the arylidene part of this series showed high activity against Gram-positive bacteria. Moreover, it is worth noting that the replacement of the furylmethylidene group in **8h** with a furoyl moiety yielded compound **9d** which, unlike **8h**, is of a moderate antibacterial activity.

Acknowledgments

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Table 2. Table 2. *In vitro* antibacterial activities of new compounds[†,‡]

Compound	*Bacillus subtilis*	*Staphylococcus aureus*	*E. coli*	*Pseudomonas aeruginosa*
3	64	>128	>128	64
5b	16	16	8	8
5f	64	>128	16	64
5h	32	32	16	16
6a	64	64	32	>128
6c	8	8	16	4
6e	32	16	32	16
6f	16	16	32	32
7	64	>128	64	64
8a	16	32	32	32
8b	1	4	4	8
8c	16	8	8	16
8d	32	32	16	16
8e	32	16	32	32
8g	64	8	32	64
8h	8	16	16	32
9b	32	32	64	64
9c	64	64	>128	64
9d	64	32	32	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 values of duplicate determinations. MIC values 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. [31]

[‡] Organisms selected: *Bacillus subtilis* ATCC 6633; *Staphylococcus aureus* ATCC 29213; *Escherichia coli* ATCC 25922; *Pseudomonas aeruginosa* ATCIC 9027.

Experimental

Chemistry

Melting points (°C, uncorrected) were determined on a Fischer-Johns apparatus (Fischer-Scientific, USA). IR spectra (KBr) were recorded on a Pye-Unicam SP1000 Spectrometer (Pye-Unicam Ltd., Cambridge, England, ν in cm^{-1}). ^1H and ^{13}C-NMR spectra were recorded on a FT-NMR specrometer (400 MHz) JNM-LA (Perkin Elmer Life and Analytical Sciences, Inc., Boston, USA) using TMS as internal standard (chemical shifts in ppm, δ units). Mass spectral data were recorded on JEOL JMS-600H spectrometer (MA, USA). The results of elemental analyses (C, H, N) were within ±0.4% of the theoretical values. Thin layer chromatography was performed on silica gel GLF plates, 250 microns.

*3-[4-(4-Aryl-3-cyano-1,2-dihydro-2-oxo-6-pyridyl)phenyl]-sydnones (**5a**–**j**)*

Method 1: A mixture of 3-[4-(3-aryl-1-oxo-2-propen-1-yl)-phenyl]sydnones **4a**–**g** (3 mmol), ethyl cyanoacetate (0.34 g, 3 mmol) and ammonium acetate (1.85 g, 24 mmol) in absolute ethanol (30 ml) was heated under reflux for 6 h. The reaction mixture was cooled to room temperature. The separated solid was filtered, dried and recrystallized from the suitable solvent. IR, **5a:** 3450 (NH), 3144 (CH, sydnone), 2216 (CN), 1754 (C=O, sydnone), 1670 (C=O), 1580 (C=N). **5e:** 3500 (NH), 3134 (CH, sydnone), 2210 (CN), 1759 (C=O, sydnone), 1702 (C=O), 1609 (C=N). **5f:** 3400 (OH), 3250 (NH), 3130 (CH, sydnone), 2213 (CN), 1745 (C=O, sydnone), 1656 (C=O), 1600 (C=N). **5h:** 3350 (NH), 3103 (CH, sydnone), 2223 (CN), 1745 (C=O, sydnone), 1638 (C=O), 1585 (C=N). **5j:** 3450 (NH), 3170 (CH, sydnone), 2216 (CN), 1754 (C=O, sydnone), 1658 (C=O), 1580 (C=N). ^1H-NMR (DMSO-d_6): **5c:** 7.28-8.40 (m, 10H, Ar-H, CH sydnone), NH seemed to be exchanged by the solvent. **5d:** 7.07-8.42 (m, 10H, Ar-H, CH sydnone). **5g:** 3.83 (s, 3H, OCH_3), 7.00-8.40 (m, 10H, Ar-H, CH sydnone), 12.85 (br s, 1H, NH; D_2O exchangeable). ^{13}C-NMR (DMSO-d_6): **5a:** 168.4 (CO, sydnone), 162.3 (CO), 159.4, 149.9, 136.3, 135.8, 130.5, 129.5, 128.8, 128.3, 121.7 (Ar C), 116.2 (CN), 98.8 (C_5, pyridine), 94.9 (CH, sydnone).

Method 2: A mixture of 3-(4-acetylphenyl)sydnone (**3**) (0.61 g, 3 mmol), the appropriate aromatic aldehyde (3 mmol), ethyl cyanoacetate (0.34 g, 3 mmol) and ammonium acetate (1.85 g, 24 mmol) in absolute ethanol (30 ml) was heated under reflux for 6 h. The reaction mixture was cooled to room temperature. The separated solid was filtered, dried and recrystallized from the suitable solvent.

Method 3: A mixture of compound **3** (0.61 g, 3 mmol), the appropriate aromatic aldehyde (3 mmol), ethyl cyanoacetate (0.34 g, 3 mmol) and ammonium acetate (1.85 g, 24 mmol) was heated in an oil bath at 140–160 °C for 30 min then cooled to room temperature. Absolute ethanol was added with stirring and the product was collected by filtration, dried and recrystallized from the suitable solvent.

*3-[4-(2-Amino-4-aryl-3-cyano-6-pyridyl)phenyl]sydnones (**6a–j**)*

Method 1: The same procedure as described in method 1 for preparation of compound **5** was applied except that malononitrile (0.20 g, 3 mmol) was used instead of ethyl cyanoacetate. IR, **6a:** 3439 (NH_2), 3126 (CH, sydnone), 2209 (CN), 1748 (C=O, sydnone), 1637 (C=N). **6b:** 3352 (NH_2), 3150 (CH, sydnone), 2211 (CN), 1752 (C=O, sydnone), 1639 (C=N). **6f:** 3350 (NH_2), 3149 (CH, sydnone), 2220 (CN), 1758 (C=O, sydnone), 1602 (C=N). ^{1}H-NMR (DMSO-d_6): **6a:** 7.28–8.38 (m, 11H, Ar-H, CH sydnone), NH_2 seemed to be exchanged by the solvent. **6c:** 6.70-7.90 (m, 10H, Ar-H, CH sydnone). **6d:** 6.77 (s, 1H, CH sydnone), 6.85-8.40 (m, 9H, Ar-H). **6e:** 3.81 (s, 3H, OCH_3), 7.07-8.42 (m, 10H, Ar-H, CH sydnone).

Method 2: The same procedure as described in method 2 for preparation of compound **5** was adopted except that malononitrile (0.20 g, 3 mmol) was used instead of ethyl cyanoacetate.

Method 3: The same procedure as described in method 3 for preparation of compound **5** was followed except that malononitrile (0.20 g, 3 mmol) was used instead of ethyl cyanoacetate.

*1-[4-(ψ-5-Oxo-1,2,3-oxadiazol-3-yl)phenyl]ethylidenehydrazine (**7**)*

Method 1: A mixture of compound **3** (2.04 g, 10 mmol), and hydrazine hydrate 99% (5 g, 0.1 mol) in absolute ethanol (30 ml) was stirred for 8 h at room temperature. The product formed was collected by filtration, dried and recrystallized from ethanol-acetone mixture to yield 1.75 g (80%) of **7**, mp 205–207 °C. IR**:** 3381 (NH_2), 3140 (CH, sydnone), 1750 (C=O, sydnone), 1637 (C=N). ^{1}H-NMR (DMSO-d_6): 1.10 (s, 3H, CH_3), 4.92 (br s, 2H, NH_2; D_2O exchangeable), 6.84-8.44 (m, 5H, Ar-H, CH sydnone).

Method 2: The same procedure as described in method 1 except that the reaction mixture was refluxed for 1 h. Further work up as described in the previous method yielded 1.85 g (85%) of **7**, mp 206–208 °C.

*2-Arylidene-1-[4-ψ-5-oxo-1,2,3-oxadiazol-3-yl)phenyl]ethylidenehydrazine (**8a–h**)*

A mixture of compound **7** (0.22 g, 1 mmol) and the appropriate aromatic aldehyde (1 mmol) in absolute ethanol (20 ml) was heated under reflux for 5 h. On cooling, the separated solid was filtered, dried and recrystallized from the suitable solvent. IR: **8a:** 3166 (CH, sydnone), 1754 (C=O, sydnone), 1615 (C=N). **8d:** 3133 (CH, sydnone), 1741 (C=O, sydnone), 1635 (C=N), 3400 (OH). **8g:** 3147 (CH, sydnone), 1760 (C=O, sydnone), 1611 (C=N). ^{1}H-NMR (DMSO-d_6): **8a:** 1.03 (s, 3H, CH_3), 6.72-8.80 (m, 11H, Ar-H, N=C-H, CH sydnone). **8c:** 1.23 (s, 3H, CH_3), 6.74–8.63 (m, 10H, Ar-H, N=C-H, CH sydnone). **8d:** 1.17 (s, 3H, CH_3), 5.22 (s, 1H, OH; D_2O exchangeable), 6.62–8.64 (m, 10H, Ar-H, N=C-H, CH sydnone). **8f:** 1.15 (s, 3H, CH_3), 6.72–8.82 (m, 9H, Ar-H, N=C-H, CH sydnone). **8g:** 1.20 (s, 3H, CH_3), 7.30–8.50 (m, 9H, Ar-H, N=C-H, CH sydnone). ^{13}C-NMR (DMSO-d_6): **8c:** 168.4 (CO, sydnone), 140.9 (CH_3-C=N), 135.8 (N=CH), 135.3, 132.9, 129.8, 128.9, 128.3, 121.3 (Ar C), 94.8 (CH, sydnone). MS, *m/z* (%), **8g:** 375 (1.1, M^+), 345 (5.2, M^+-NO), 317 (63.8, M^+-CNO_2), 290 (7.2, $C_{15}H_{12}Cl_2N_2$), 144 (26.5, $C_9H_8N_2$),117 (46.1, C_8H_7N), 101 (100, C_7H_3N), 76 (97.5, C_6H_4).

*2-Aroyl-1-[4-(ψ-5-oxo-1,2,3-oxadiazol-3-yl)phenyl]ethylidenehydrazine (9a-d) and Bis-[1-[4-(ψ-5-oxo-1,2,3-oxadiazol-3yl)-phenyl]ethylidenehydrazinocarbonyl]methane (**10**)*

A mixture of 3-(4-acetylphenyl)sydnone (**3**) (2.04 g, 10 mmol), and the appropriate acid hydrazide (10 mmol) in absolute ethanol (30 ml) was heated under reflux for 8 h. The reaction mixture was cooled to room temperature, the formed precipitate was filtered, dried and recrystallized from the suitable solvent. IR: **9a:** 3311 (NH), 3120 (CH, sydnone), 1775 (C=O, sydnone), 1662 (C=O, amide), 1588 (C=N). **9b:** 3450 (OH), 3325 (NH), 3139 (CH, sydnone), 1729 (C=O, sydnone), 1676 (C=O, amide), 1602 (C=N). **9d:** 3325 (NH), 3116 (CH, sydnone), 1738 (C=O, sydnone), 1668 (C=O, amide), 1588 (C=N). 10: 3334 (NH), 3100 (CH, sydnone), 1744 (C=O, sydnone), 1683 (C=O, amide), 1600 (C=N). ^{1}H-NMR (DMSO-d_6): **9a:** 1.19 (s, 3H, CH_3), 6.69–8.31 (m, 10H, Ar-H, CH sydnone), 10.13 (br s, 1H, NH; D_2O exchangeable). **9c:** 1.12 (s, 3H, CH_3), 6.74–8.23 (m, 9H, Ar-H, CH sydnone), 10.79 (br s, 1H, NH; D_2O exchangeable). MS, *m/z* (%), **9a:** 292 (5.7, M^+-NO), 264 (50.2, M^+-CNO_2), 237 (0.9, $C_{15}H_{13}N_2O$), 131 (8.9, $C_8H_7N_2$), 105 (100, C_7H_5O), 77 (82.9, C_6H_5).

Antibacterial Activity

The synthesized compounds were evaluated for their *in vitro* antibacterial activity against representative Gram-positive and Gram-negative organisms applying standard agar dilution method using Mueller-Hinton medium. MICs 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. The 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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