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Synthesis of benzaldehyde substituted phenyl carbonyl hydrazones and their formylation using Vilsmeier-Haack reaction

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Abstract: A series of benzaldehyde substituted phenyl carbonyl hydrazones has been synthesized and their formylation has been carried out by using Vilsmeier-Haack reaction. All the hydrazones and their formyl derivatives were screened for antibacterial activity.
Key words: Vilsmeier-Haack reaction, formylation, hydrazones, C-formyl hydrazones, N-formyl hydrazones.

Introduction

Formylation is a key process in organic synthesis in which the resulting aldehyde function acts as a 'crossroads' intermediate, hence a large number of methods have been developed for this reaction. Many formylation reactions use reagents for formylation are mostly of the type Y-CH-$X^{\oplus}$.Such reactions are Vilsmeier ($ClCH=NR_2^+$), Rieche (eg.$MeOCHCl_2 \rightarrow MeO=CHCl^+$), Gatterman ($Zn[CN]_2$ / $HCl \rightarrow HC = NH_2^{2+}$), Gatterman-Koch (CO/HCl/Lewis acid $\rightarrow HC=O^+$) & even Duff ($CH_2= NH_2^+$– Followed by dehydrogenation of initially formed R CH_2 NH_2)[1].

The Vilsmeier- Haack reaction[2] is widely used for formylation. It can be applied to introduce an aldehyde group on activated aromatic compounds & olefinic compounds. The formylderivative obtained can further react to afford more complex molecules to be used as building blocks in biological active compounds, supramolecular chemistry & molecular electronics[3-22]. Many other conversions can be achieved with this technology.

A large number of heterocyclic Schiff bases have been reported to have bactericidal[23-25], fungicidal[23-24], antipyretic[25], antitumour[26], antitubercular[27], anticancer[28-36] and sterease inhibitory activities. Some of the Schiff bases were used as chelating agents[30, 31], analytical reagents[32] for transition metal analysis and used as catalyst for epoxidation of olefins[33]. Schiff bases and farmazons have shown antiviral[37], antimicrobial[38] and anti-inflammatory activities[39]. Schiff bases and their metal complexes exhibit a wide spectrum of physiological and pharmacological activities[40]. Schiff bases and other products from 4-N, N-biscyano ethyl amino benzaldehyde have shown a high degree of anticancer activity. Schiff bases bearing chloro moiety have pronounced pesticidal activities[41-43].

As a result of these useful properties, a large number of Schiff bases have been developed. Considering these applications it was planed to synthesize Benzaldehyde – phenyl / substituted phenyl carbonyl hydrazones (Schiff bases) with the hope to get some Schiff bases of interesting biological activities.

The starting compounds required for the preparation of Schiff bases are hydrazides ($RCONHNH_2$). Most of the reported procedures for the preparation of hydrazides, especially α, β unsaturated hydrazides are low yielding and require chromatographic purification which is not suitable for large scale preparations.

Hydrazides can be synthesized by hydrazinolysis of amides, esters and thioesters[44]. The reaction of hydrazines with acylchlorides or anhydrides is also well known[45].

In the present work we have developed an efficient and general process, involving preforming activated esters or amides followed by reaction with hydrazine, for the preparation of hydrazides. This process gave the desired hydrazides in excellent yield and purity under mild conditions.

Initially esters were prepared from 4-hydroxybenzoic acid, 4-chlorobenzoic acid, 2-chlorobenzoic acid and benzoic acid by using the method reported by S.D. Bhardwaj[46].The refluxion on these acids with absolute methanol and conc. H_2SO_4 on steam bath formed corresponding methyl substituted benzoates **2a** m.p. 130 ^{0}C (70%), **2b** m.p. 43 ^{0}C (75%), **2c** b.p. 232 ^{0}C (65%) and **2d** b.p. 197 ^{0}C (85%). These compounds were characterized by their similarity of physical constants **2a** 130 ^{0}C, **2b** 43 ^{0}C, **2c** 232 ^{0}C and **2d** 197 ^{0}C with reported[47] **2a** 131 ^{0}C, **2b** 44 ^{0}C, **2c** 234 ^{0}C and **2d** 199 ^{0}C.

The methyl esters 2a-d on refluxing in water bath with hydrazine hydrate dissolved in methanol formed corresponding benzhydrazides **3a** m.p. 260-262 ^{0}C (68%), **3b** m.p. 162 ^{0}C (72%), **3c** m.p. 109 ^{0}C (52%) and **3d** m.p. 110 ^{0}C (74%). These hydrazides were characterized by their similarity of physical constants **3b** 162 ^{0}C, **3c** 109 ^{0}C, and **3d** 111 ^{0}C with reported[48] (**Scheme-I**).

Condensation of 4-hydroxybenzhydrazide (**3a**) with 4-methoxybenzaldehyde, 4-hydroxybenzaldehyde, 2-nitro benzaldehyde and benzaldehyde respectively in methanol containing catalytic amount of acetic acid formed 4-methoxybenzaldehyde -4-hydroxyphenyl-1-carbonyl hydrazone (**4a**) in 55.55% yield, m.p. 216-218 ^{0}C, 4-hydroxybenzaldehyde -4-hydroxyphenyl-1-carbonylhydrazone (**4b**) in 68.32% yield, m.p. 250-252 ^{0}C, 2-nitrobenzaldehyde -4-hydroxyphenyl-1-carbonylhydrazone (**4c**) in 79.68% yield, m.p. 258-260 ^{0}C and benzaldehyde -4-hydroxyphenyl-1-carbonylhydrazone (**4d**) in 62.50% yield, m.p. 228-230 ^{0}C.

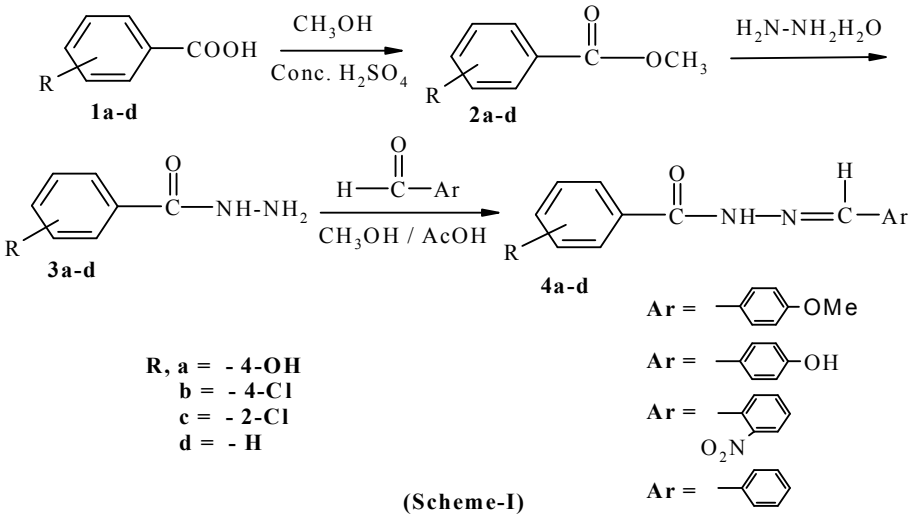
Condensation of 4-chlorobenzhydrazide (**3b**) with 4-methoxybenzaldehyde, 4- hydroxybenzaldehyde, 2-nitro benzaldehyde and benzaldehyde respectively in methanol containing catalytic amount of acetic acid formed 4-methoxybenzaldehyde -4-chlorophenyl-1-carbonyl hydrazone (**5a**) in 95.48% yield, m.p. 174-176 ^{0}C, 4-hydroxybenzaldehyde -4-chlorophenyl-1-carbonylhydrazone (**5b**) in 94.73% yield, m.p. 290-291 ^{0}C, 2-nitrobenzaldehyde -4-chlorophenyl-1-carbonylhydrazone (**5c**) in 72.49% yield, m.p. 234-235 ^{0}C and benzaldehyde -4-chlorophenyl-1-carbonylhydrazone (**5d**) in 96.0% yield, m.p. 248-250 ^{0}C.

Condensation of 2-chlorobenzhydrazide (**3c**) with 4-methoxybenzaldehyde, 4- hydroxybenzaldehyde, 2-nitro benzaldehyde and benzaldehyde respectively in methanol containing catalytic amount of acetic acid formed 4-methoxybenzaldehyde -2-chlorophenyl-1-carbonyl hydrazone (**6a**) in 90.0% yield, m.p. 100-120 ^{0}C, 4-hydroxybenzaldehyde -2-chlorophenyl-1-carbonylhydrazone (**6b**) in 87.0% yield, m.p. 208-210 ^{0}C, 2-nitrobenzaldehyde -2-chlorophenyl-1-carbonylhydrazone (**6c**) in 94.0% yield, m.p. 220-222 ^{0}C and benzaldehyde -2-chlorophenyl-1-carbonylhydrazone (**6d**) in 92.0% yield, m.p. 155-157 ^{0}C.

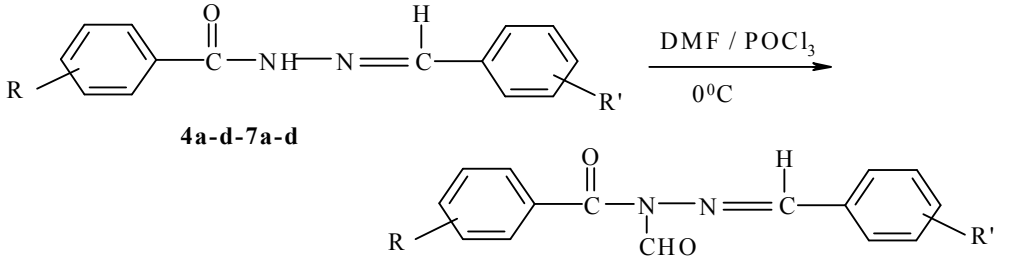
Condensation benzhydrazide (**3d**) with 4-methoxybenzaldehyde, 4- hydroxybenzaldehyde, 2-nitro benzaldehyde and benzaldehyde respectively in methanol containing catalytic amount of acetic acid formed 4-methoxybenzaldehyde phenyl-1-carbonyl hydrazone (**7a**) in 65.35% yield, m.p. 145-147 ^{0}C, 4-hydroxybenzaldehyde phenyl-1-carbonylhydrazone (**7b**) in 69.35% yield, m.p. 225-227 ^{0}C, 2-nitrobenzaldehyde phenyl-1-carbonylhydrazone (**7c**) in 79.92% yield, m.p. 185-186 ^{0}C and benzaldehyde phenyl-1-carbonylhydrazone (**7d**) in 89.28% yield, m.p. 220-221 ^{0}C. In the synthesis of these Schiff's bases we got excellent yields.

It was decided to formylate benzaldehyde hydrazones (**4a-d – 7a-d**) by using Vilsmeier-Haack reagent with the hope to get formylated benzaldehyde hydrazones as visualized in (**Scheme-II**).

The formylation reaction of benzaldehyde hydrazones **4** with DMF/$POCl_3$ at 0 ^{0}C followed by stirring reaction mixture at 60-65 ^{0}C for 4 hrs and neutralization with $NaHCO_3$ formed formyl derivatives in which formyl group was introduced at nitrogen or at carbon atom as proposed in the following mechanisms.

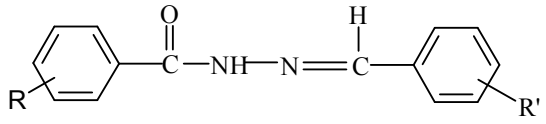


(Scheme-I)

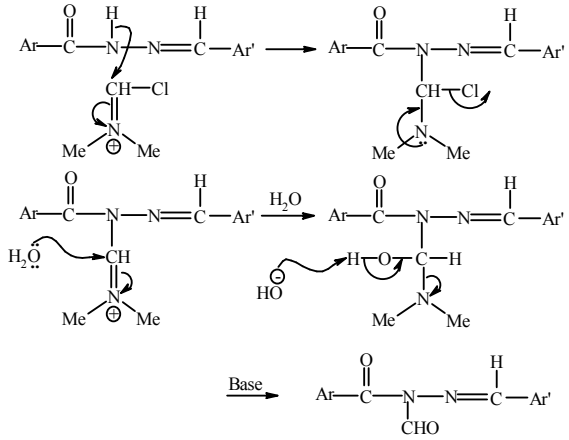


R= -4-OH **a, R'= -4-OH**
R= -4-Cl **b, R'= -4-OCH_3**
R= -2-Cl **c, R'= -H**
R= -H **d, R'= -2-NO_2**

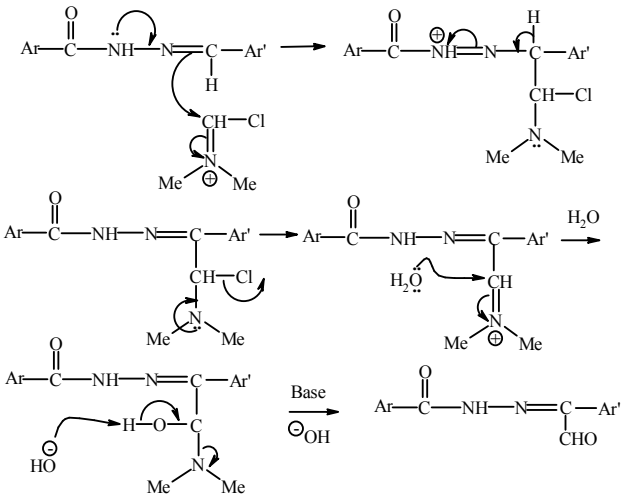
(Scheme-II)



4, R= -4-OH **a, R'= -4-OMe**
5, R= -4-Cl **b, R'= -4-OH**
6, R= -2-Cl **c, R'= -2 -NO_2**
7, R= -H **d, R'= -H**

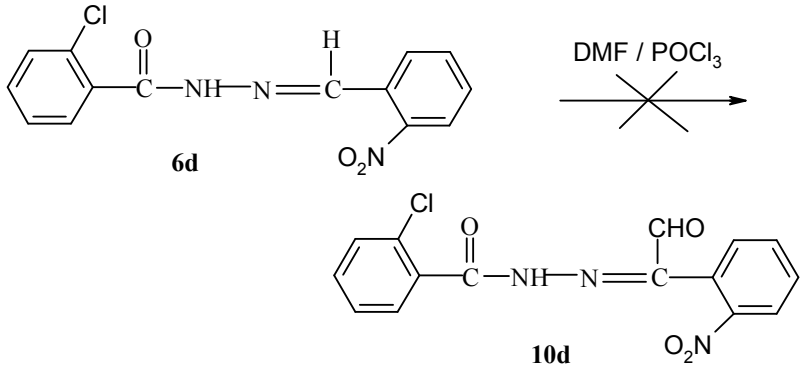


Formylation at N-atom (Cyclisation is not possible)



Formylation at C-Center only (Cyclisation is not possible)

After carrying out these reactions and studying spectral data we found that compounds **4a-c, 5a-c, 6a-c, 7a-c** undergo formylation at N-atom while in compounds **4d, 5d** and **7d** formylation takes place at C-atom. In all these cases $-NO_2$ group is situated at ortho position. [1] H-NMR of compound **4a-c** showed absence of N-H proton while in the compounds obtained from **4d**, **5d** and **7d** – NH proton was found present. In these compounds =CH proton was found absent indicating the presence of –CHO group at that carbon atom. We have also noted one important point in these formylation reactions, we could not get N-formylated or C-formylated product when compound **6d** was treated with $DMF/POCl_3$ we have attempted this reaction several times by changing parameters such as change in reaction time, change in temperature and change in molarities of reagents, even then we failed to get the desired formylated product.



6d **10d**

Biological testing of the compounds

All the synthesized compounds **4a-d, 6a-d, 7a-d, 8a-d, 10a-c, 11a-d** were evaluated in-vitro for antibacterial activity against bacterial strains *Proteus vulgaris, Staphylococcus aureus, Salmonella typhimurium* at the concentrations 1 mg/ml by paper disc diffusion method using DMF as solvent and nutrient agar as culture media. The results were obtained in the form of clearing zone and were noted after the period of incubation (37 ^{0}C for 24-48 hrs). The zones of inhibition were measured in mm and the data is presented in **table-I**.

Similarly compounds **5a-d** and **9a-d** were evaluated in-vitro for antibacterial activity against bacterial strains *E. coli* and *S. aureus* at the conc. 1 mg/ml by paper disc diffusion method using DMF as solvent. The data is presented in **table-II**.

Results

The compounds **4a, 4c, 4d, 6a, 6d, 7a, 7b, 7c** were found to be active against *P. vulgaris*. Other compounds were found inactive against *P. vulgaris*, *S. aureus,* and *S. typhimurium*. Compounds **5a, 5b, 9b, 9c** and **9d** showed significant activity against *S. aureus* where as **5d, 9a, 9b** and **9d** were found active against *E. coli* (**Table-I & Table-II**)

Experimental section

Melting points were determined in open capillary tube and are uncorrected. IR spectra were recorded on Perkin-Elmer Spectrophotometer in KBr pellets and Nujol Mull for solid compounds. The PMR spectra were recorded in DMSO-d_6 +$CDCl_3$ or $CDCl_3$ on Brucker-400MHg FT-NMR instrument or Perkin-Elmer R-32 (90 MHz) instrument using TMS as an internal standard (Chemical shift in δ ppm). Elemental analysis was carried out using Eager 200 windows method.

Thin layer chromatography was run on silica gel G for TLC and spots were visualized by iodine vapour or by irradiation with ultraviolet light.

1-(3-4-hydroxyphenyl-N-formyl-1-carbonyl)4-hydroxybenzene hydrazone (8a)

To the Vilsmeier-Haack complex prepared from DMF (10 ml) and $POCl_3$ (1.1 ml, 0.012 mole) at 0 ^{0}C was added the hydrazone **4a** (1.02 gm, 0.004 mole) and the reaction mixture was stirred at 60-65 ^{0}C for 4 hrs and poured into ice cold water. The product separated on neutralization with $NaHCO_3$ was filtered and recrystallized from aq. methanol.

Yield 1.024 gm (44.64%), m.p. 118-120 ^{0}C,
I.R: 3223, 2854, 1643, 1608, 1462 cm^{-1}.
^{1} H-NMR (DMSO-d_6): δ 7.4 (1H, S, -CHO), 1.20 (1H, S, -CH), 9.35 (1H, S, -OH), 6.89-6.87 (4H, M, -Ar), 6.85-6.83 (4H, M, -Ar)
Elemental analysis calculated for $C_{15}H_{12}N_2O_4$, C 63.38, H 4.12, N 9.85, found C 63.22, H 4.15, N 9.73%

Compounds **8b-d, 9a-d, 10a-c** and **11 a-d** were prepared by using above method starting from corresponding hydrogens **4b-d, 5a-d, 6a-c, 7a-d** respectively.

1-(3-4-methoxybenzaldehyde-N-formyl-1-carbonyl) 4-hydroxybenzene hydrazone (8b)

Yield 1.08 gm (33.35%), m.p. 158-160 ^{0}C,
I.R: 3120, 2854, 1640, 1609, 1442, 1258 cm^{-1}.
^{1} H-NMR (DMSO-d_6): δ 7.84 (1H, S, -CHO), 1.20 (1H, S, -CH), 2.89 (3H, S, -OCH_3), 9.20 (1H, S, -OH), 6.80-6.76 (4H, M, -Ar), 6.54-6.50 (4H, M, -Ar)

1-(3,benzaldehyde-N-formyl-1-carbonyl)4-hydroxybenzene hydrazone (8c).

Yield 0.96 gm (31.70%), m.p. 100-101 ^{0}C,
I.R: 3200, 2856, 1646, 1609, 1456.94 cm^{-1}.
^{1} H-NMR (DMSO-d_6): δ 7.73 (1H, S, -CHO), 1.09 (1H, S, -CH), 9.40 (S, 1H, -OH), 6.94-6.64 (M, 4H, -Ar), 5.90-5.86 (M, 5H, -Ar)

1-(3, 2-nitrobenzaldehyde-C-formyl-1-carbonyl) 4-hydroxybenzene hydrazone (8d).

Yield 1.14 gm (43.02%), m.p. 115-117 ^{0}C,
I.R: 3230.39, 2854.89, 1644.40, 1667, 1462.43, 1351.28, 1547.20 cm^{-1}.
^{1} H-NMR (DMSO-d_6): δ 7.79 (S, 1H, -CHO), 9.30 (S, 1H, -OH), 10.97 (S, 1H, -N-N), 5.85-5.81 (M, 4H, -Ar), 7.04-6.77 (M, 4H, -Ar)

1-(3-4-hydroxybenzaldehyde-N-formyl-1-carbonyl) 4-chlorobenzene hydrazone (9a).

Yield (30.02%), m.p. 120 ^{0}C,
I.R. (KBr): 3413.39, 2790, 1693.19. 1655, 1509.99 cm^{-1}.

1-(3-4-methoxybenzaldehyde-N-formyl-1-carbonyl) 4-chlorobenzene hydrazone (9b).

Yield (56.47%), m.p. 102 ^{0}C,
I.R. (KBr): 2832.92, 1680, 1620, 1259.29, 1432.85 cm^{-1}.

1-(3-benzaldehyde-N-formyl-1-carbonyl)4-chlorobenzene hydrazone (9c).

Yield (31.40%), m.p. 120 ^{0}C,
I.R. (KBr): 2820, 1650, 1656.55, 1656 cm^{-1}.

1-(3-2-nitrobenzaldehyde-C-formyl-1-carbonyl)4-chlorobenzene hydrazone (9d).
Yield (23.91%), m.p. 115 ^{0}C,
I.R. (KBr): 3010, 2830, 1692, 1655, 1536.99 cm^{-1}.

1-(3-4-hydroxybenzaldehyde-N-formyl-1-carbonyl) 2-chlorobenzene hydrazone (10a).
Yield (15.00%), m.p. 80 ^{0}C,
I.R. (KBr): 3330.10, 2810, 1685.20, 1650, 1510.15 cm^{-1}.

1-(3-4-methoxybenzaldehyde-N-formyl-1-carbonyl) 2-chlorobenzene hydrazone (10b).
Yield (15.00%), m.p. 110 ^{0}C,
I.R. (KBr): 2820, 1690, 1649.50, 1521.29, 1271.30 cm^{-1}.

1-(3-benzaldehyde-N-formyl-1-carbonyl)2-chlorobenzene hydrazone (10c).
Yield (20.16%), m.p. 90 ^{0}C,
I.R. (KBr): 2854, 1685, 1652, 1524.29 cm^{-1}.

1-(3-4-hydroxybenzaldehyde-N-formyl-1-carbonyl) benzene hydrazone (11a).
Yield (39.00%), m.p. 85-87 ^{0}C,
I.R. (KBr): 2844.31, 2735.73, 1643, 1604.60, 1454.23 cm^{-1}.

1-(3-4-methoxybenzaldehyde-N-formyl-1-carbonyl) benzene hydrazone (11b).
Yield (61.57%), m.p. 108-110 ^{0}C,
I.R. (KBr): 2840.95, 1666.38, 1612.38, 1429.15, 1215.07 cm^{-1}.

1-(3-benzaldehyde-N-formyl-1-carbonyl)benzene hydrazone (11c).
Yield (32.00%), m.p. 110-111 ^{0}C,
I.R. (KBr): 2842, 1640, 1610, 1432.30 cm^{-1}.

1-(3-benzaldehyde-C-formyl-1-carbonyl)benzene hydrazone (11d).
Yield (22.00%), m.p. 72-73 ^{0}C,
I.R. (KBr): 2848, 1649, 1612, 1419, 1554, 1342 cm^{-1}.

Conclusion

In this work we have developed a general method for the synthesis of benzhydrazides and benzaldehyde hydrazones with good yields which can be used for preparing different heterocyclic systems. The 4-hydroxy Benzhydrazide and all the other benzaldehyde hydrazones are so far unknown synthones which could be used for preparing various heterocyclic systems.

Formylation of benzaldehyde hydrazones using DMF/$POCl_3$ formed C-terminal or N-terminal formylated products without cyclisation with comparatively low yields.

Table I: Antibacterial activity of compounds, ZONE of inhibition (m.m.):

Compound	*P. Vulgaris*	*S. aureus*	*S. typhimurium*
4a	08	-	-
4b	-	-	-
4c	06	-	-
4d	08	-	-
6a	10	-	-
6b	-	-	-
6c	-	-	-
6d	10	-	-
7a	11	-	-
7b	12	-	-
7c	08	-	-
7d	-	-	-
8a	08	-	-
8b	14	-	-
8c	20	-	-
8d	14	09	-
10a	22	-	-
10b	-	-	-
10c	-	-	-
11a	-	-	-
11b	-	-	-
11c	-	-	-
11d	-	-	-

Table II: Antibacterial activity of compounds, zone of inhibition (mm):

Compound	*E. coli*	*S. aureus*
5a	-	12
5b	-	10
5c	-	-
5d	08	-
9a	07	-
9b	10	12
9c	-	06
9d	08	10

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