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Note

Antimicrobial activity of 1-[*p*{3′-(2′-aryl-4-oxo-1′,3′-thiazolyl)} diphenyl]/[3′-(2′-aryl-4-oxo-1′,3′-thiazolyl)]-2-phenyl-4-cyclohexylidene imidazol-5-ones

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2-Phenyl-4-cyclohexylidene-1,3-oxozol-5-one **1** has been obtained from the condensation of hippuric acid and cyclohexane using acetic anhydride. The compound **1** is then converted to its respective imidazoles **2** and **3** by condensing with benzidene and hydrazine hydrate. Which on heating with different aromatic aldehydes give 1-(*p*-arylidene-amino-diphenyl)/(arylidene-amino)-2-phenyl-4-cycohexlyidene imidazol-5-one **4** and **5**. Interaction of **4** and **5** with thioglycollic acid undergo cyclization to give titled compounds **6** and **7**. The new compounds have been screened for their antimicrobial activity.

Keywords: Oxozolone, hippuric acid, cyclohexane, acetic anhydride, imidazole, thioglycollic acid

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Thiazole are familiar group of heterocyclic compounds possessing a wide variety of biological activities and their utility as medicaments is very much established[1-4]. Thiazole nucleus is also integral part of all the available penicillins which have revolutionized the therapy of bacterial diseases[5-10]. A detailed literature survey[11,12] reveals a large number. of thiazole derivatives containing other hetero cyclic systems have been designed, synthesized and evaluated for their antimicrobial activity involving several strains of bacteria, fungi and viruses[13-16]. Also imidazoles are important group of compounds that are of great importance in medicinal chemistry[17-20]. Various compounds having a modified imidazolidine ring possessed quite good antiviral activity[9]. Prompted by these reports and in continuation of our work on heterocycles as antimicrobial agents, we report in this paper the synthesis and antimicrobial activity of 1-[*p*{3′-(2′-aryl-4–oxo-1′,3′-thiazolyl)} diphenyl]/[-3′-(2′-aryl-4-oxo-1′,3′-thiazolyl)]-2-phenyl-4-cyclohexylidene imidazol-5-ones.

Antimicrobial screening

Compounds **6a-e** and **7a-e** were screened for their antibacterial activity against *Escherichia coli* and *Bacillus subtilis in vitro* involving the two fold serial dilution technique as recommended by the National Committee for Clinical Laboratory Standards (NCCLS)[10]. The activity data for all compounds tested is presented in **Table I**.

Antimicrobial activity data for compounds **6a-e** are suggestive of unsuitablility of such compounds as for as against highly pathogenic strain of *E. coli* is concerned since only one compound was found to show a marginal degree of activity. Out of five compounds only one compound **5a** having a *p*-Cl substituent was found to exhibit very low order of antimicrobial activity since MIC obtained was 50.

Antimicrobial data of compounds **6a-e** against *B. subtilis* are also suggestive of either very weak activity or non existent activity of such compounds since only two compounds showed very low order of antimicrobial activity. Here, both the compounds bearing hydroxyl function at *ortho* and *para* position displayed the same order of activity.

Only one compound of the type imidazolyl thiazolyles **7a-d** displayed highly satisfactory activity against *E. coli.* Other three compounds were found inactive at the same concentration. Thus, the compound **7a** had MIC value of 6.25 µg/mL while for other three compounds the MIC values are very high. It is interesting to observe here that an electronegative group present (R = *p*-Cl) at the *para* position seems mainly responsible for causing a change in the activity since for *o*-OH substituted compound the MIC obtained was >100. There may be two ways to explain these results. First, *p*-Cl substituted compound is able to penetrate the cell wall of *E. coli* thus preventing the biosynthesis of the polymer peptidoglycan or secondly it is finding better fit at the receptor site as compared to other three compounds.

On evaluation for their antimicrobial activity against *B. subtilis* compound **7a-d** furnished some very valuable results. Two of the four compounds of this category were found to inhibit the growth of bacteria to a considerable extent while two others were found least significant. The compound **7d** is highly active. This compound bearing a *o*-nitro substituent has displayed a comparable activity since

Table I — Antimicrobial activities of compounds **6a-e** and **7a-d** and standard antibiotics

Compd	R	Minimum inhibitory concentration (MIC) μg/mL against *E. coli*	Compd	R	Minimum inhibitory concentration (MIC) μg/ mL against *B. subtilis*
6a	*p*-Chlorophenyl	50	**7a**	*p*-Chlorophenyl	12.5
6b	*o*-Hydroxyphenyl	75	**7b**	*o*-Hydroxyphenyl	>100
6c	*p*-Hydroxyphenyl	75	**7c**	*p*-Hydroxyphenyl	50
6d	Phenyl	>100	**7d**	*o*-Nitrophenyl	3.175
6e	4-OH, 3-OCH_3-Phenyl	>100	**7e**	Carbenicillin	>200
6f	Amoxycillin	>100			

MIC was found to be 3.175 μg/mL while compound **7a** showed a comparatively diminished activity (MIC 12.5μg/mL). These results can be interpreted in terms of electronic factors. Nitro group has a –I and +R effect from these positions. However, more study is required involving the synthesis of additional compounds bearing more electronegative group and subjecting these new chemical candidate molecules for their *in vitro* and *in vivo* assessment against same and other bacterial strain.

Experimental Section

2-Phenyl-4-cyclohexylidene-1,3-oxazol-5-one 1 (refs 11,12). A mixture of cyclohexanone (0.03 mole), hippuric acid (0.03 mole), acetic anhydride (20 mL) and anhydrous sodium acetate (0.03 mole), was stirred mechanically and refluxed on a water-bath for 2 hr. Subsequently, 100 mL ethanol was added to it and allowed to stand overnight. A yellow solid which separated out, was filtered off and washed successively with cold water. It was recrystallized from benzene. m.p. 168°C, yield 80%.

1-(*p*-Amino diphenyl/amino-2-phenyl-4-cyclohexylidene imidazol)-5-ones 2 and 3. A mixture of (0.05 mole) and 1,1-biphenyl-4,4-diamine (0.05 mole) in anhydrous pyridine (50 mL) was heated under reflux on a sand-bath for 6 hr under anhydrous conditions. Subsequently, the reaction mixture was poured into ice-cold water (100 mL) containing conc. HCl (10 mL). A solid started to separate out, was allowed to settle down for 1 hr. It was filtered off and washed sucessessively with water, dried and recrystallized from ethanol to give **2**, m.p. 240°C, yield 75%.

For the synthesis of compound **3a**, mixture of **1** and hydrazine hydrate (0.025 mole) in ethanol (50 mL) was heated under reflux for 4 hr. Ethanol was distilled off and the residual solid thus obtained was washed with solvent. It was dried at 100°C and recrystallized from dilute methanol as pale yellow crystals, m.p. 152°C, yield: 70%.

1-(*p*-Arylidenoamino diphenyl/arylidenoamino-2-phenyl-4-cyclohexylidene imidazol-5-ones 4a-e, 5a-d. A mixture of imidazole **2** (0.02 mole) and (0.02 mole) of an appropriate arylaldehyde in absolute EtOH (30 mL) in the presence of gl. acetic acid (1 mL) was refluxed for 8-10 hr. Excess of solvent was removed under reduced pressure and solid obtained was washed with cold water several times and recrystallized from methanol **(Table II)**.

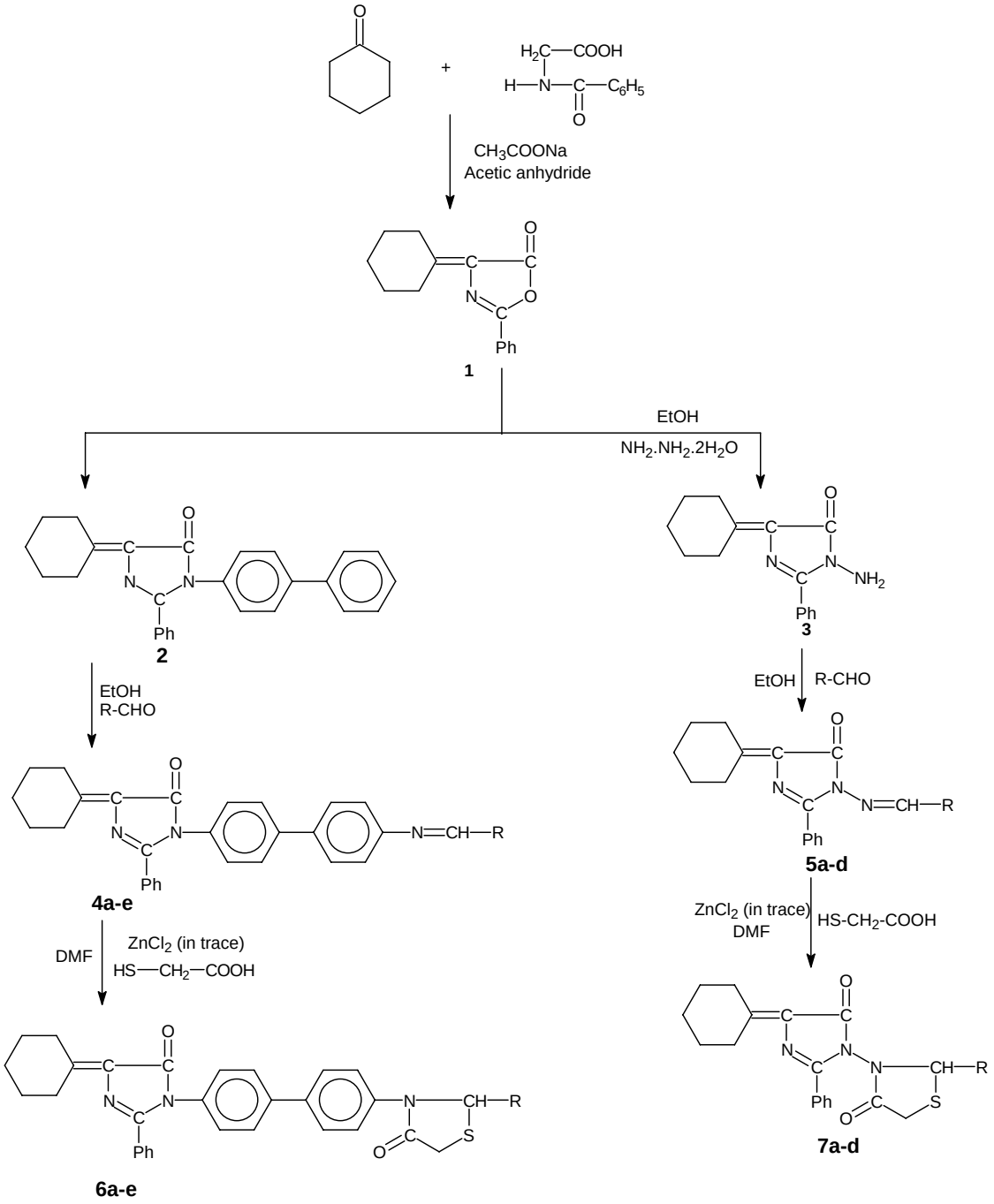
4c: ^{1}H NMR($CDCl_3$): δ 1.22-2.76 (m, 10H, CH_2 in ring), 4.76 (s, 1H, N-CH-R), 6.76-7.95 (m, 17H, Ar-H), 5.12 (s, 1H, Ar-OH).

5c: ^{1}H NMR ($CDCl_3$): δ 2.1-2.72 (m, 10, CH_2 in ring), 4.48 (s, 1H, -N-CH-R), 6.40-7.86 (m, 9H, Ar-H), 5.22 (s, 1H, Ar-OH).

4-1-[*p*{3′-(2′-Aryl- 4 - oxo-1′,3′-thiazolyl)}diphenyl]/[-3′-(2′-aryl-4-oxo-1′,3′-thiazolyl)]- 2 - phenyl-cyclohexylidene imidazol-5-one 6a-e, 7a-d. A mixture of compound **4** or **5** (0.01 mole), thioglycollic acid (0.01 mole) containing $ZnCl_2$ (in trace) in dimethylformamide (DMF) was heated under reflux for 4 hr. It was poured into crushed ice and stirred vigorously. Solidification occurred after fifteen minutes. It was filtered off and washed with cold water. Recrystallization from ethanol gave analytically pure sample **(Scheme I, Table II)**.

6a: ^{1}H NMR ($CDCl_3$): δ 6.69-7.71 (m, 17H, Ar-H), 4.91 (br s, 1H, S, replaceable-OH), 1.2-2.39 (m, 10H, CH_2 in ring), 3.32 (s, 1H, $-N-\underset{\underset{S}{|}}{CH}-Ar$), 3.58 (s, 2H, O=C-$CH_2$-S).

6b: ^{1}H NMR ($CDCl_3$,): δ 6.63-7.89 (m, 17H, Ar-H), 4.89 (br s, 1H, s, replaceable-OH), 1.4-2.51 (m, 10H, CH_2 in ring), 3.29 (s, 1H, $-N-\underset{\underset{S}{|}}{CH}-Ar$), 3.39 (s, 2H, O=C-$CH_2$-S).



Scheme I

Table II — Characterization data for compounds **4a-e, 5a-d, 6a-e** and **7a-d**

Compd.	R	m.p. °C	Yield (%)	Mol. formula	Nitrogen Found % (Calcd)
4a		255	60	$C_{34}H_{28}N_3OCl$	7.91 (7.93)
5a	*p*-Chlorophenyl	171	85	$C_{22}H_{20}N_3OCl$	11.12 (11.14)
6a		175	80	$C_{36}H_{30}N_5O_2SCl$	6.92 (6.96)
7a		98	80	$C_{24}H_{23}N_3O_2SCl$	9.27 (9.31)

Contd

Table II — Characterization data for compounds **4a-e, 5a-d, 6a-e** and **7a-d** — *Contd*

Compd.	R	m.p. °C	Yield (%)	Mol. formula	Nitrogen Found % (Calcd)
4b	*o*-Hydroxyphenyl	238	75	$C_{34}H_{29}N_3O_2$	8.18 (8.21)
5b		218	55	$C_{22}H_{21}N_3O_2$	11.66 (11.69)
6b		120	72	$C_{36}H_{31}N_3O_3S$	7.14 (7.17)
7b		87	70	$C_{24}H_{23}N_3O_3S$	9.58 (9.69)
4c	*p*-Hydroxyphenyl	254	80	$C_{34}H_{29}N_3O_2$	8.18 (8.21)
5c		245	80	$C_{22}H_{21}N_3O_2$	11.66 (11.69)
6c		237	60	$C_{36}H_{31}N_3O_3S$	7.12 (7.17)
7c		168	80	$C_{24}H_{23}N_3O_3S$	9.58 (9.69)
4d	Phenyl	176	65	$C_{34}H_{29}N_3O$	8.44 (8.48)
6d		227	55	$C_{36}H_{31}N_3O_2S$	7.35 (7.38)
5d	*o*-Nitrophenyl	182	65	$C_{22}H_{20}N_4O_3$	14.35 (14.43)
7d		110	68	$C_{24}H_{22}N_4O_4S$	12.10 (12.12)
4e	4-OH, 3-OCH_3-phenyl	182	50	$C_{35}H_{31}N_3O_3$	7.73 (7.76)
6e		171	75	$C_{37}H_{33}N_3O_4S$	6.79 (6.84)

6c: ^{1}H NMR ($CDCl_3$): δ 6.71-7.62 (m, 17H, ArH), 4.82 (br s, 1H, s, replaceable –OH), 1.0-2.48 (m, 10H, CH_2 in ring), 3.38 (s, 1H, $-N-\underset{\underset{S}{|}}{CH}-Ar$), 3.69 (s, 2H, O=C–$CH_2$–S); Mass (FAB): 585 ($M^+$), 569, 465, 508, 391, 194, 557, 529, 426, 89, 91 (base peak).

6d: ^{1}H NMR ($CDCl_3$): δ 1.38-2.61 (m, 10H, CH_2 in ring), 3.42 (s, 2H, O=C–CH_2–S), 3.39 (s, 1H, $-N-\underset{\underset{S}{|}}{CH}-Ar$); Mass (FAB): 569 ($M^+$), 492, 391, 465, 419, 512, 89, 91 (base peak).

6e: ^{1}H NMR ($CDCl_3$): δ 1.09-2.43 (m, 10H, CH_2 in ring), 3.81 (s, 2H, O=C–CH_2–S), 3.55 (s, 1H, $-N-\underset{\underset{S}{|}}{CH}-Ar$); Mass (FAB): 690 ($M^+$), 585, 391, 560, 588, 569, 485, 457, 391, 225, 91 (base peak).

7a: ^{1}H NMR ($CDCl_3$): δ 1.16-2.9 (m, 10H, CH_2 in ring), 3.41 (s, 2H, O=C–CH_2–S), 4.66 (s, 1H, N–CH–R), 6.66-7.59 (m, 9H, Ar-H); Mass (FAB): 451/453 (M^+): 239, 211, 416, 89, 91, 374/376, 318/320, 340, 104 (base peak).

7b: ^{1}H NMR ($CDCl_3$): δ 1.19-2.72 (m, 10H, CH_2 in ring), 3.62 (s, 2H, O=C-CH_2-S), 4.59 (s, 1H, N–CH–R); Mass (FAB): 433(M^+), 239, 416, 367, 329, 301, 109, 211, 89, 91 (base peak).

7c: ^{1}H NMR ($CDCl_3$): δ 1.21-2.85 (m, 10H, CH_2 in ring), 3.59 (s, 2HO=C–CH_2–S), 4.84 (s, 1H, –N–CH–R), 5.11 (brs, 1H, s, replaceable –OH), 6.75-7.92 (m, 9H, Ar-H).

7d: ^{1}H NMR ($CDCl_3$): δ 1.27-2.81 (m, 10H, CH_2 in ring), 3.73(s, 2H, O=C-CH_2-S), 4.64(s, 1H, CH-R), 6.81-7.94 (m, 9H, Ar-H); Mass (FAB): 462 (M^+), 211, 239, 416, 385, 357, 329, 340, 239, 89 (base peak).

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