

# Synthesis and Pharmacological Studies of Aminoxy Containing 2,4,6-Trisubstituted-s-Triazine Derivatives

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Arylamines on diazotization and further treatment with dicyandiamide yielded aryldicyandiamide (1a-d), which on addition with aminoxy compound (2) gave corresponding biguanides (3a-d). Cycloaddition of biguanide with ethylchloroacetate furnished 2,4,6-trisubstituted-s-triazines (4a-d). Subsequent treatment of these compounds with N-hydroxyphthalimide or N-hydroxysuccinimide in presence of triethylamine gave final compounds (5a-h). IR, <sup>1</sup>H NMR and mass spectra were used to confirm their structure. Compounds (5a-h) were screened for antibacterial (*Escherichia coli*, *Proteus vulgaris*, *Klebsiella pneumoniae*, *Pseudomonas aureus* and *Staphylococcus aureus*) and antifungal (*Candida albicans* and *Aspergillus fumigatus*) activities. Antibacterial activity revealed that compounds 5a, 5b, 5c, 5g showed comparable activity against bacteria *P. vulgaris*, *P. aureus*, where rest of the compounds showed weak activity against all the pathogenic bacteria. The fungicidal data indicated that compound 5d possess high level activity and rest of the compounds showed comparable to the standard.

In the present communication, a series of 2-(2',4'-dinitroarylaminoxy)-4-methoxyphthalimido or methoxysuccinimido-6-(4"-subs.anilino)-s-triazine (5a-h) have been synthesized and tested for antimicrobial activities. The synthesis of s-triazine<sup>1</sup> and their pharmacological applications<sup>2-5</sup> are well documented. Some 2-arylamino-4-chloro-6-(pyrimidine-4-carboxyhydrazino)-1,3,5-triazines have been synthesized<sup>6</sup> and observed to possess remarkable antitubercular activity. Several derivatives of s-triazine show antimicrobial<sup>7</sup>, antibacterial<sup>8</sup> and herbicidal<sup>9</sup> activities. These are also used for treatment of HIV infection<sup>10</sup>. Phthalimidoxy derivatives represent one of the most active class of compounds possessing biological activities<sup>11,12</sup>. N-phthalimidoxy-2-methacrylate, ethyl N-phthalimidoxy acetate containing phthalimidoxy group have been demonstrated to possess anticancer<sup>13</sup>, anticonvulsant<sup>14</sup>, antimalarial<sup>15</sup>, hypotensive<sup>16</sup> and antiamebic<sup>17</sup> properties. Aminoxy moiety has a special place in the modern therapy of malaria<sup>18</sup>. Synthesis and antimicrobial properties of substituted 3-aminoxy propionyl and 3-aminoxy (E)-2-methoxyimino propionyl monolactams have been reported<sup>19</sup>. Combination of all these three biological moieties in one molecule might result in the overall enhanced biological activity.

## MATERIALS AND METHODS

Melting points of synthesized compounds were determined in open capillary tubes and are therefore uncorrected. The structures of compounds were established on the basis of elemental analysis and spectral data. The IR spectra were recorded in the range of 4000-450 cm<sup>-1</sup> using KBr pellets on a FTIR RXI Perkin-Elmer spectrophotometer. <sup>1</sup>H NMR spectra were recorded on a Bruker DRX 300 MHz spectrophotometer using CDCl<sub>3</sub>/DMSO-d<sub>6</sub> as solvent. The FAB mass spectra were recorded on a Jeol SX-102/DA-6000 spectrometer data system using argon/xenon (6KV,10 mA) as FAB gas. Purity of synthesized compounds was checked by silica gel-G plates of 2 mm thickness using benzene and ethyl acetate (9:1 and 1:9) as solvent system and iodine chamber as developer. N-Hydroxyphthalimide was prepared by reported method<sup>20</sup>.

### 4-Substituted aryl dicyandiamide (1a-d):

Suspension of p-substituted aniline (0.01 mol) in hot 5 N HCl was cooled to 0-5°. It was diazotized by adding sodium nitrite (0.01 mol) solution in water, whether the reaction has completed or not was checked by starch-iodide paper<sup>21</sup>. Diazotized mixture was slowly added to a solution of dicyandiamide (0.01 mol) in water (25 ml) with stirring,

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maintaining the temperature at 0-5°. Anhydrous sodium carbonate was added in small quantities during 2 h to maintain alkalinity of the reaction. Triazine obtained was washed with water and dried. This was then added during half an hour to a stirred mixture of DMF (50 ml) and 10 N HCl (20 ml) at 30-35°. This reaction mixture was further stirred for half an hour. Water was added to obtain a precipitate. Crude product was crystallized from methanol. Similarly other compounds (1b-d) were prepared.

#### 2,4-Dinitrophenoxamine hydrochloride (2):

2,4-Dinitrochlorobenzene (0.01 mol) in DMF was added to a stirred solution of N-hydroxyphthalimide (0.01 mol) in DMF. Reaction mixture was stirred at room temperature for 5-6 h and then left for overnight. It was filtered and the filtrate was poured in ice cold water. Product 2,4-dinitrophenoxaphthalimide(2) obtained was recrystallized from alcohol and hydrolyzed by dissolving it in glacial acetic acid and boiled with hydrobromic acid (37%) for 20-30 min. Phthalic acid separated on cooling was filtered, solvent was removed under reduced pressure. Crude solid was washed with petroleum ether.

#### N<sup>1</sup>-(2,4-Dinitroaryloxy)-N<sup>5</sup>-(4'-substituted aryl) biguanides (3a-d):

A mixture of (1a, 0.01 mol) was refluxed with (2, 0.01 mol) in absolute alcohol for 7-8 h. It was filtered and the filtrate was diluted with water. Sodium bicarbonate was added to it till turbidity appears. It was left for 10 h at room temperature. Crude product obtained was recrystallized from dilute methanol. Other compounds (3 b-d) were prepared by similar method with slight variation in refluxing time.

#### 2-(2',4'-Dinitroaryloxyamino)-4-(chloromethyl)-6-(4''-substituted anilino)-s-triazine (4a-d) :

To a stirred solution of (3a, 0.01 mol) in methanol, sodium (0.01 mol) was added. It was further stirred for 20 min, after this ethylchloroacetate (0.01 mol) was added. It was stirred further for 24 h<sup>22</sup>. After evaporation of the solvent and recrystallization from absolute alcohol, yellow-brown crystals were obtained. Similarly other compounds (4b-d) were also prepared with minor modification in mole ratio of reagents and stirring period.

#### 2-(2',4'-Dinitroaryloxyamino)-4-methoxyphthalimido or methoxysuccinimido-6-(4''-substituted anilino)-s-triazine (5a-h):

To a stirred solution of (4a, 0.01 mol) in DMF, a solution of N-hydroxyphthalimide (0.01 mol) in DMF was added in presence of TEA (0.02 mol) as a base. It was further stirred

for 24 h. It was filtered and the filtrate was poured in crushed ice. Crude product obtained was recrystallized from absolute alcohol. Compounds (5b-h) were also synthesized by similar method using reagents in proper mole ratio. The entire synthetic route has been shown in scheme 1.

#### Characteristics of 5a:

IR (KBr,  $\nu_{\max}$  in  $\text{cm}^{-1}$ ) : 3455 (NH str.), 3080 (Ar-H), 2892 ( $\text{CH}_2$ ), 1700 (CO-N-CO), 1615 (C=N), 1510, 1300 ( $\text{NO}_2$ ), 1280 (C-N), 1120 (C-O), 980 (N-O), 740 (C-Cl); PMR (DMSO- $d_6$ ,  $\delta$  in ppm): 8.0 (m, 3H, Ar-H, near  $\text{NO}_2$ ), 7.4 (d, 2H, Ar-H, near Cl), 7.1-6.9 (m, 6H, Ar-H), 6.7 (s, 1H, NH-O), 4.8 (s, 1H, NH), 3.6 (s, 2H,  $\text{CH}_2$ -O); m/z : 580  $[\text{M}+2]^+$ , 578  $[\text{M}]^+$ , 395, 268, 122, 106, 92, 66, 40.

#### Characteristics of 5b:

IR (KBr,  $\nu_{\max}$  in  $\text{cm}^{-1}$ ) : 3471 (NH str.), 3067 (Ar-H), 2960 ( $\text{CH}_3$ ), 2874 ( $\text{CH}_2$ ), 1712 (CO-N-CO), 1603 (C=N), 1500, 1399 ( $\text{NO}_2$ ), 1121 (C-O), 935 (N-O); PMR (DMSO- $d_6$ ,  $\delta$  in ppm): 8.1 (m, 3H, Ar-H, near  $\text{NO}_2$ ), 7.1 (m, 8H, Ar-H), 6.7 (s, 1H, NH-O), 4.8 (s, 1H, NH), 3.5 (s, 2H,  $\text{CH}_2$ -O), 2.2 (s, 3H,  $\text{CH}_3$ ); m/z : 558  $[\text{M}]^+$ , 375, 268, 122, 106, 66, 40.

#### Characteristics of 5c:

IR (KBr,  $\nu_{\max}$  in  $\text{cm}^{-1}$ ) : 3420 (NH str.), 3085 (Ar-H), 2888 ( $\text{CH}_2$ ), 1708 (CO-N-CO), 1610 (C=N), 1510 ( $\text{NO}_2$ ), 1120 (C-O), 995 (N-O), 580 (C-Br); PMR (DMSO- $d_6$ ,  $\delta$  in ppm): 8.0 (m, 3H, Ar-H, near  $\text{NO}_2$ ), 7.2 (m, 8H, Ar-H), 6.7 (s, 1H, NH-O), 4.8 (s, 1H, NH), 3.6 (s, 2H,  $\text{CH}_2$ -O); m/z : 614  $[\text{M}+1]^+$ , 613  $[\text{M}]^+$ , 449, 268, 122, 100, 40.

#### Characteristics of 5d:

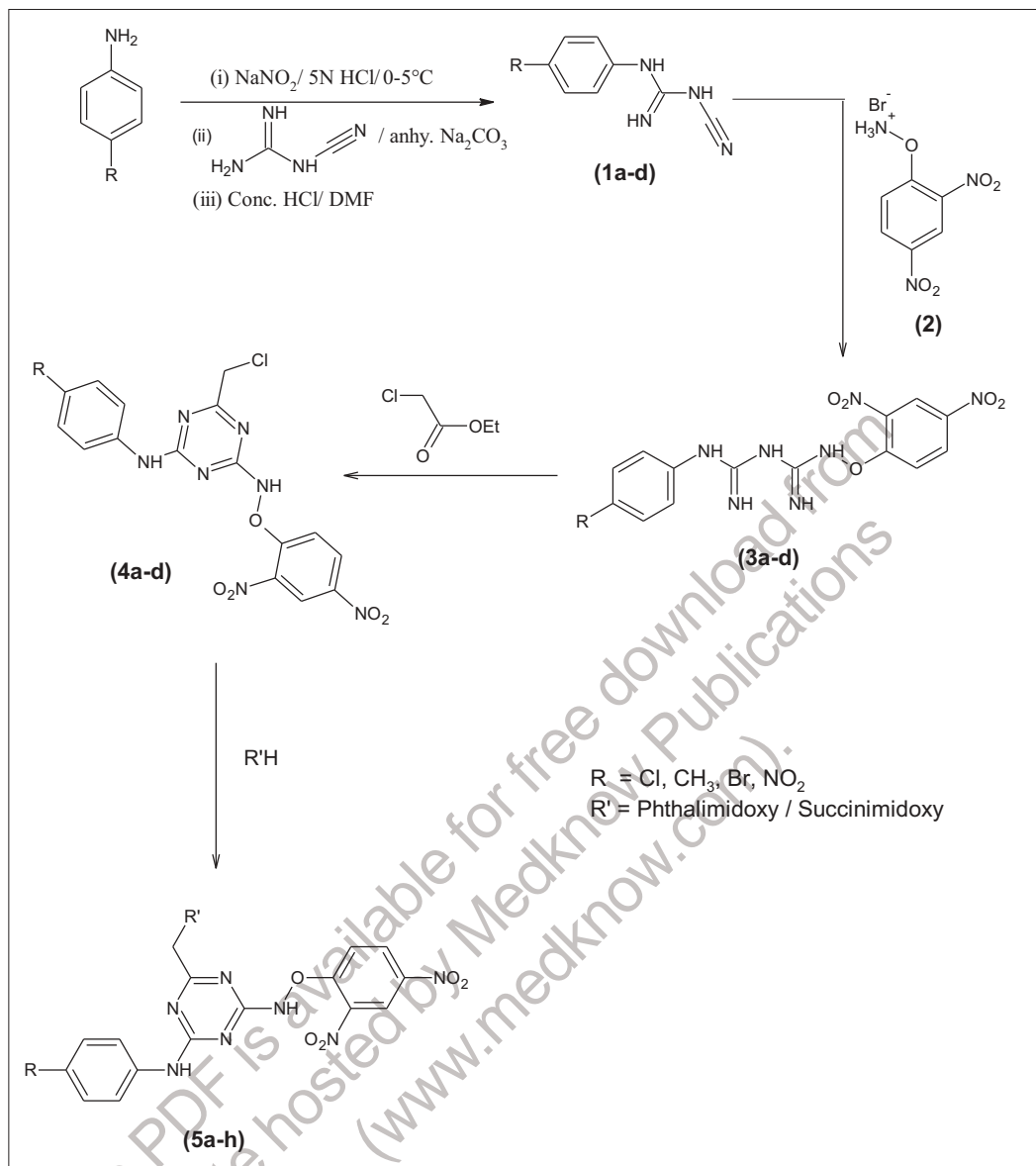
IR (KBr,  $\nu_{\max}$  in  $\text{cm}^{-1}$ ) : 3450 (NH str.), 3090 (Ar-H), 2890 ( $\text{CH}_2$ ), 1690 (CO-N-CO), 1675 (C=N), 1510, 1300 ( $\text{NO}_2$ ), 1275 (C-N), 1120 (C-O), 920 (N-O); PMR (DMSO- $d_6$ ,  $\delta$  in ppm): 8.1 (m, 7H, Ar-H, near  $\text{NO}_2$ ), 7.1 (m, 4H, Ar-H), 6.7 (s, 1H, NH-O), 4.9 (s, 1H, NH), 3.6 (s, 1H,  $\text{CH}_2$ -O); m/z : 589  $[\text{M}]^+$ , 406, 268, 122, 106, 66, 40.

#### Characteristics of 5e:

IR (KBr,  $\nu_{\max}$  in  $\text{cm}^{-1}$ ) : 3445 (NH), 3080 (Ar-H), 2895 ( $\text{CH}_2$ ), 1680 (CO-N-CO), 1625 (C=N), 1500 ( $\text{NO}_2$ ), 750 (C-Cl); PMR (DMSO- $d_6$ ,  $\delta$  in ppm): 8.0 (m, 3H, Ar-H, near  $\text{NO}_2$ ), 7.4 (d, 2H, Ar-H, near Cl), 7.0 (d, 2H, Ar-H, near NH), 6.8 (s, 1H, NH-O), 4.8 (s, 1H, NH), 3.5 (s, 1H,  $\text{CH}_2$ -O), 2.2 (t, 4H,  $\text{CH}_2$ -CO); m/z : 532  $[\text{M}+2]^+$ , 530  $[\text{M}]^+$ , 432, 416, 402, 275, 92, 78, 52, 26.

#### Characteristics of 5f:

IR (KBr,  $\nu_{\max}$  in  $\text{cm}^{-1}$ ) : 3440 (NH), 2990 ( $\text{CH}_3$ ), 2880 ( $\text{CH}_2$ ), 1670 (CO-N-CO), 1610 (C=N), 1500 ( $\text{NO}_2$ ); PMR



**Scheme 1: Synthetic scheme of aminoxy containing 2,4,6-trisubstituted-s-triazine derivatives.**

(DMSO- $d_6$ ,  $\delta$  in ppm): 8.0 (m, 3H, Ar-H, near  $\text{NO}_2$ ), 7.2 (m, 4H, Ar-H), 6.7 (s, 1H, NH-O), 4.7 (s, 1H, NH), 3.5 (s, 1H,  $\text{CH}_2$ -O), 2.3 (s, 3H,  $\text{CH}_3$ ), 2.2 (t, 4H,  $\text{CH}_2$ );  $m/z$ : 510  $[\text{M}]^+$ , 412, 396, 382, 275, 92, 78.

#### Characteristics of 5g:

IR (KBr,  $\nu_{\text{max}}$  in  $\text{cm}^{-1}$ ): 3430 (NH), 2890 ( $\text{CH}_2$ ), 1690 (CO-N-CO), 1630 (C=N), 1510 ( $\text{NO}_2$ ), 550 (C-Br); PMR (DMSO- $d_6$ ,  $\delta$  in ppm): 8.1 (m, 3H, Ar-H, near  $\text{NO}_2$ ), 7.2 (m, 4H, Ar-H), 6.7 (s, 1H, NH-O), 4.6 (s, 1H, NH), 3.6 (s, 1H,  $\text{CH}_2$ -O), 2.3 (t, 4H,  $\text{CH}_2$ );  $m/z$ : 575  $[\text{M}+1]^+$ , 574  $[\text{M}]^+$ , 476, 460, 446, 275, 92, 26.

#### Characteristics of 5h:

IR (KBr,  $\nu_{\text{max}}$  in  $\text{cm}^{-1}$ ): 4450 (NH), 2892 ( $\text{CH}_2$ ), 1695

(CO-N-CO), 1638 (C=N), 1500, 1310 ( $\text{NO}_2$ ); PMR (DMSO- $d_6$ ,  $\delta$  in ppm): 8.2 (m, 7H, Ar-H, near  $\text{NO}_2$ ), 6.9 (s, 1H, NH-O), 4.8 (s, 1H, NH), 3.8 (s, 1H,  $\text{CH}_2$ -O), 2.4 (t, 4H,  $\text{CH}_2$ );  $m/z$ : 541  $[\text{M}]^+$ , 443, 427, 413, 275, 78.

#### Antimicrobial activity:

Antimicrobial activity was assayed by well or cup method<sup>23</sup> in nutrient agar and Sabourand dextrose agar. Media was inoculated with 0.2 ml suspension of organisms by spread plate method<sup>24</sup>. With the help of sterile borer, a well was made in the centre of medium and filled with 300  $\mu\text{g}/\text{ml}$  concentration of synthesized compounds. The incubation time was 24 h at 37° for bacteria and 74 h at 37° for fungal strains. Antimicrobial activity was measured as a function of diameter of zone of inhibition (mm). The

results were compared to ampicillin and levofloxacin for antibacterial activity and fluconazole for antifungal activity by measuring zone of inhibition in mm at 300 µg/ml concentration using disc diffusion method<sup>25</sup>.

## RESULTS AND DISCUSSION

Diazotization of 4-substituted arylamine in presence of NaNO<sub>2</sub> and 5N HCl at 0-5° and subsequent treatment of dicyandiamide in alkaline medium yielded 4-substituted aryl dicyandiamide (1a-d). The formation of compound (1a) was confirmed on the basis of spectral data. IR data reveals the presence of NH stretching at 3450, C≡N stretching at 2250 and C=N stretching at 1680 cm<sup>-1</sup>. Furthermore, the presence of singlet at δ 4.5 ppm of NH confirmed the formation of compound (1a). Compounds (1a-d) when treated with aminoxy compound (2) in alcoholic medium yielded corresponding biguanides (3a-d). Formation of compound (3a) was confirmed by the disappearance of C≡N peak at 2250 cm<sup>-1</sup> and appearance of NO<sub>2</sub> peak at 1500, 1350 cm<sup>-1</sup> and multiplet at δ 8.0 ppm (DMSO) for the aryl proton near NO<sub>2</sub>. Cycloaddition of compounds (3a-d) with ethylchloroacetate in presence of sodium furnished 2,4,6-trisubstituted-s-triazine (4a-d). Structure of 4a was confirmed by the appearance of C-Cl peak at 740 and CH<sub>2</sub> peak at 2890 cm<sup>-1</sup>. Compounds (4a-d) were lastly condensed with N-hydroxyphthalimide or N-hydroxysuccinimide in presence of TEA to obtain final compounds (5a-h). Disappearance of C-Cl peak at 740 and

appearance of CO-N-CO peak at 1712 cm<sup>-1</sup> confirmed the structure of compounds (5a-h). Melting points, yields and elemental analysis of these compounds are given in Table 1.

The synthesized compounds (5a-h) were tested *in vitro* for antibacterial and antifungal activities against *Escherichia coli*, *Proteus vulgaris*, *Klebsiella pneumoniae*, *Pseudomonas aureus*, *Staphylococcus aureus*, *Candida albicans* and *Aspergillus fumigatus* (Table 2).

The synthesized compounds at 300 µg/ml concentration showed low antibacterial activity as compared to the standard ampicillin and levofloxacin while these also found to show good antifungal activity as compared to the standard fluconazole. All the compounds were found to be more active towards *Aspergillus fumigatus* than *Candida albicans*. It can be concluded from antimicrobial activity that combination of all the three biological moieties i.e., phthalimidoxy, aminoxy and s-triazine in one molecule results in the enhancement of biological activity.

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TABLE 1: PHYSICAL AND ANALYTICAL DATA OF SYNTHESIZED COMPOUNDS

Compd.	R	R'	Mol. Formula/Mol. Wt.	mp (°)	Yield (%)	% of N Calc./ found
1a	Cl	-	C <sub>8</sub> H <sub>7</sub> N <sub>4</sub> Cl/194.5	201	60	28.79/28.52
1b	CH <sub>3</sub>	-	C <sub>9</sub> H <sub>10</sub> N <sub>4</sub> /174	211	75	32.18/31.90
1c	Br	-	C <sub>8</sub> H <sub>7</sub> N <sub>4</sub> Br/229	219	50	24.45/23.10
1d	NO <sub>2</sub>	-	C <sub>8</sub> H <sub>7</sub> N <sub>5</sub> O <sub>2</sub> /205	245	67	34.14/34.00
2	-	-	C <sub>6</sub> H <sub>5</sub> N <sub>3</sub> O <sub>5</sub> /199	120	40	21.10/21.05
3a	C1	-	C <sub>14</sub> H <sub>12</sub> N <sub>7</sub> O <sub>5</sub> C1/393.5	234	50	24.90/24.82
3b	CH <sub>3</sub>	-	C <sub>15</sub> H <sub>15</sub> N <sub>7</sub> O <sub>5</sub> /373	220	70	26.27/26.10
3c	Br	-	C <sub>14</sub> H <sub>12</sub> N <sub>7</sub> O <sub>5</sub> Br/428	198	35	22.89/22.24
3d	NO <sub>2</sub>	-	C <sub>14</sub> H <sub>12</sub> N <sub>8</sub> O <sub>7</sub> /404	208	25	27.72/27.52
4a	C1	-	C <sub>16</sub> H <sub>11</sub> N <sub>7</sub> O <sub>5</sub> C1 <sub>2</sub> /451	196	40	21.72/21.50
4b	CH <sub>3</sub>	-	C <sub>17</sub> H <sub>14</sub> N <sub>7</sub> O <sub>5</sub> C1/431.5	200	45	22.71/22.65
4c	Br	-	C <sub>16</sub> H <sub>11</sub> N <sub>7</sub> O <sub>5</sub> Br/496.5	210	40	19.73/19.62
4d	NO <sub>2</sub>	-	C <sub>16</sub> H <sub>11</sub> N <sub>8</sub> O <sub>7</sub> C1/462.5	190	32	24.21/24.15
5a	C1	Phthali-midoxy	C <sub>24</sub> H <sub>15</sub> N <sub>8</sub> O <sub>8</sub> C1/578.5	222	40	19.36/19.25
5b	CH <sub>3</sub>	"	C <sub>25</sub> H <sub>18</sub> N <sub>8</sub> O <sub>8</sub> /558	256	45	20.07/19.68
5c	Br	"	C <sub>24</sub> H <sub>15</sub> N <sub>8</sub> O <sub>8</sub> Br/614	238	30	18.27/17.65
5d	NO <sub>2</sub>	"	C <sub>24</sub> H <sub>15</sub> N <sub>9</sub> O <sub>10</sub> /589	164	28	21.39/19.00
5e	C1	Succini-midoxy	C <sub>20</sub> H <sub>15</sub> N <sub>8</sub> O <sub>8</sub> C1/530.5	198	42	21.11/21.01
5f	CH <sub>3</sub>	"	C <sub>21</sub> H <sub>18</sub> N <sub>8</sub> O <sub>8</sub> /510	208	40	21.96/21.94
5g	Br	"	C <sub>20</sub> H <sub>15</sub> N <sub>8</sub> O <sub>8</sub> Br/575	188	32	19.47/19.40
5h	NO <sub>2</sub>	"	C <sub>20</sub> H <sub>15</sub> N <sub>9</sub> O <sub>10</sub> /541	170	30	20.70/20.68

TABLE 2: RESULTS OF ANTIMICROBIAL STUDIES OF COMPOUNDS ZONE OF GROWTH INHIBITION

Compounds	Antibacterial activity (300 µg/ml)					Antifungal activity (300 µg/ml)	
	<i>E. coli</i>	<i>P. vulgaris</i>	<i>K. pneumoniae</i>	<i>P. aureus</i>	<i>S. aureus</i>	<i>A. fumigatus</i>	<i>C. albicans</i>
5a.	12	20	13	19	8	20	26
5b.	10.2	17	13.6	21	10	24	19
5c.	11	18	12	20	12	22	22
5d.	14	18.5	14	17	9	26	20
5e.	9	15	12.2	14	7	21	20
5f.	13.5	18	15	18	8.2	23	21
5g.	14	17	12	20	6	20	23
5h.	12	13	12.5	15	8	19.5	25
Amicacin*	23	21	23	21	28	-	-
Levofloxacin*	21	23	26	23	25	-	-
Fluconazole*	-	-	-	-	-	25	30

\*Diameter of disc in 5 mm

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