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Contributed Paper

A Facile Synthesis of Diaylureas and Their Antimicrobial Evaluation

Sundaramoorthy Sarveswari and Vijayaparthasarathi Vijayakumar*
Centre for Organic and Medicinal Chemistry, School of Advanced Sciences, VIT University, Vellore-632014, Tamil Nadu, India.
*Author for correspondence; e-mail: kvpsvijayakumar@gmail.com

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ABSTRACT

A series of the diaryl ureas were synthesized from aryl amines by phosgene free protocol. They were screened for their anti microbial activity. The anti microbial activities were not promising towards all the tested organisms. But the compound 3h and 3k were shown comparable activity against *Proteus mirabilis* with respect to the standard ciprofloxacin.

Keywords: aryl amines, one pot synthesis, microwave assisted synthesis, conventional synthesis, anti microbial activity

1. INTRODUCTION

Diaryl ureas are important class of compounds with diverse biological activity. To explain the role of diaryl urea pharmacophore some of the reports on biological activities of diaryl ureas and bio-isosteric interaction of this pharmacophore with the target were reported [1-3]. They found to act as a potential Raf kinase inhibitors [4-5] and antagonists of human vanilloid receptor1 (VR 1) [6] Phenyl thiazolyl urea derivatives have been reported as inhibitors of Murine receptor A and Murine receptor B [7]. Some substituted ureas are used as antidiabetic and tranquilizing drugs, antioxidants in gasoline, corrosion inhibitor and herbicides [8].

Some urea derivatives were found to potentially mimic the structure of combretastatin A-4 [9]. It was reported that N-phenyl-N′-(2-chloroethyl) ureas (CEU) as antimicrotubule agents and their mode of action has been explained. According to their report CEU binds covalently to the colchicine-binding site through a nucleophilic substitution involving the N′-(2-chloroethyl) urea pharmacophore. The substituents on diaryl ureas are also playing major role in the Raf-1 kinase activity. Lyons and their co-workers reported [10] that Raf-1 kinase as a validated target for the treatment of cancer. The allosteric binding mode of a diaryl urea with p38 MAP kinase included key hydrogen bond interactions of the urea N-H bonds with Glu71 of the enzyme. These interactions were proved to be consistent with the necessity for the urea functionality in a few isoindolinone series [11-12] identified that piperidine-4-ylurea **1** (Figure1), provided excellent potency against both the human and CXCR3 receptors.

The chemokine receptor CXCR3 is a potential target for treatment of inflammatory diseases such as multiple sclerosis, asthma and rheumatoid arthritis.

Some of the patent reports on synthesis and biological activities on diarylureas are adding the importance to our focus of solvent free synthesis of similar compounds. The conventional methods reported for the synthesis of arylureas are essentially based on phosgene and isocyanates, carbamates, phosgene substitutes, carbonates, carboxylic acid derivatives and aniline [13-14.] Phosgene and isocyanates are expensive, hazardous and toxic chemicals to handle. There is a continuing interest in the simple phosgene-free rapid synthesis of diarylureas. In view of the above, we report a microwave assisted synthesis of N, N′-diarylureas **3a-k** (Scheme 1) from various primary aryl amines and ethyl acetoacetate [15]. The conventional method involves five hours of reflux [15] using zeolite HSZ-360 catalyst, whereas in this developed method the diarylureas has been synthesized within 4-16 min without any supporting agents or catalysts under the microwave irradiation. In continuation of our earlier interest in the synthesis of diarylureas, herein we report the detailed NMR spectral characterization, the plausible mechanism of formation of diarylureas and their anti microbial activities. The anti microbial activities were not promising towards all the tested organisms. But the compound **3h** and **3k** were shown comparable activity against *Proteus mirabilis* with respect to the standard ciprofloxacin. The physical data such as yield, power level and melting point of compounds **3a-k** (Table 1) are given in experimental section.

2. MATERIALS AND METHODS

2.1 General Synthetic Procedure and Spectral Data of N, N′-diarylureas

A mixture of substituted aniline **1** (0.05 *M*) and ethylacetoacetate **2** (6.5 mL, 0.05 *M*) was taken in a conical flask and irradiated under microwave at 450 W for 15 min. The reaction mixture was cooled and poured onto ethanol. The crude product formed was filtered, dried and recrystallized using ethanol.

2.1.1 N, N′-diphenylurea (3a): White solid; Melting Point: 236-38 °C; IR (KBr) cm^{-1}: 3320 (NH), 1647 (C=O), 1607 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.07 (m, 4H), 6.98 (m, 4H), 6.91 (m, 2H); Mass (EI): m/z = 212 $[M]^+$.

2.1.2 N, N′-*bis*(3-chlorophenyl)urea (**3b**): White solid; Melting Point: 234-35 °C; IR (KBr) cm^{-1}: 3291 (NH), 1635 (C=O), 1607 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.95 (NH, 2H), 7.71 (d, 2H, J = 1.8 Hz), 7.20-7.30 (m, 4H), 7.05 (dt, 2H, J = 1.8 Hz, 7.2 Hz). Mass (EI): m/z = 281 $[M+1]^+$.

2.1.3 N, N′-*bis*(2-methoxyphenyl)urea (**3c**): White solid; Melting Point: 220-22 °C; IR (KBr) cm^{-1}: 3219 (NH), 1647 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.87 (NH, 2H), 8.10 (dd, 2H, J = 7. 2 Hz, J = 1.6 Hz), 7.00 (dd, 2H, J = 8.0 Hz, 1.4 Hz), 6.95 (dt, 2H, J = 7.4 Hz, 1.6 Hz), 6.89 (dt, 2H, J = 7.7 Hz, 1.4 Hz), 3.80 (s, 6H, -OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 224.09, 152.57, 139.75, 128.74, 121.80, 118.26; Mass (EI): m/z = 273 $[M+1]^+$.

2.1.4 N, N′-*bis*(4-methoxyphenyl)urea (**3d**)**:**.White solid; Melting Point: 224-26 °C; IR (KBr) cm^{-1}: 3209 (NH), 1642 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.35 (s, NH, 2H), 7.32 (d, 4H, J = 8.9 Hz), 6.84 (d, 4H, J = 8.9 Hz), 3.7 (s, 6H,-OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 154.32, 152.93, 132.91, 119.89, 113.93; Mass (EI):

m/z = 273 $[M+1]^+$.

2.1.5 N, N′-*bis*(2-methlyphenyl)urea (**3e**)**:** White solid; Melting Point: 235-36 °C; IR (KBr) cm^{-1}: 3304 (NH), 1641 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.23 (s, NH, 2H) 7.80 (d, 2H, *J* = 7.8 Hz), 7.10 - 7.3 (m, 4H), 6.97 (t, 2H, *J* = 4.0 Hz), 1.3 (s, 6H, -CH_3); Mass (EI): m/z = 238 $[M-2]^+$.

2.1.6 N, N′-*bis*(3-methylphenyl)urea (3f): White solid; Melting Point: 236-37 °C; IR (KBr) cm^{-1}: 3298 (NH), 1635 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.30 (s, NH, 2H) 7.80 (d, 2H, *J* = 7.8 Hz), 7.13 - 7.19 (m, 4H), 6.90 (t, 2H, *J* = 4.0 Hz), 2.3 (s, 6H, -CH_3); Mass (EI): m/z = 238 $[M-2]^+$.

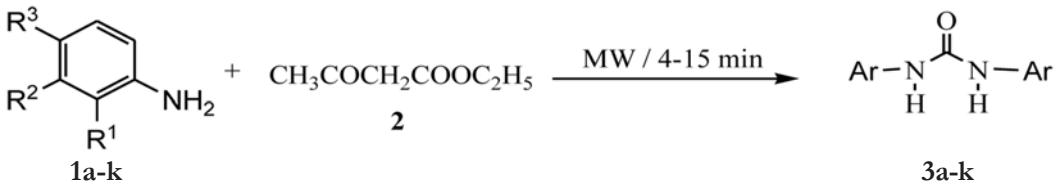
2.1.7 N, N′-*bis*(4-fluorophenyl)urea (3g): White solid; Melting Point: 246-48 °C; IR (KBr) cm^{-1}: 3295 (NH), 1631 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.40 (dt, 4H, *J* = 9.0 Hz, 4.0 Hz), 7.31 (dt, 4H, *J* = 9.0 Hz, 2.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 161.35, 158.96, 136.61, 122.45, 116.36; Mass (EI): m/z = 248 $[M]^+$.

2.1.8 N, N′-*bis*(2-chloro-4-flourophenyl) urea (**3h**): Pale brown solid; Melting Point: 228-31 °C; IR (KBr) cm^{-1}: 3321 (NH), 1657 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.93 (s, NH, 2H), 7.67 (dd, 2H, *J* = 6.5 Hz, 2.6 Hz), 7.24-7.32 (m, 2H), 7.15 (t, 2H, *J* = 8.9 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 156.36, 154.91, 154.02, 137.47, 122.23, 121.65, 121.45, 121.11, 120.30, 117.61, 117.40, 109.44; Mass(EI): m/z = 316 $[M]^+$.

2.1.9 N, N′-*bis*(4-nitrophenyl)urea (**3i**): White solid; Melting Point: 236-38 °C; IR (KBr) cm^{-1}: 3344 (NH), 1650 (C=O), 1498 (NO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.66 (s, NH, 2H), 8.00 (d, 4H, *J* = 9.2 Hz), 8.20 (d, 4H, *J* = 9.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 205.24, 163.95, 143.28, 124.99, 119.51; Mass (EI): m/z =302 $[M]^+$.

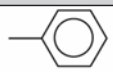
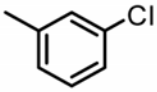
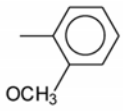
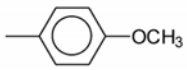
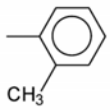
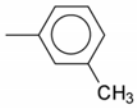
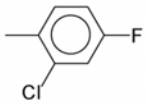
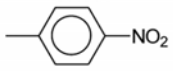
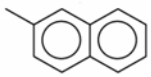
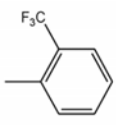
2.1.10 N, N′-*bis*(naphthyl)urea (**3j**): White solid; Melting Point: 264-65 °C; IR (KBr) cm^{-1}: 3279 (NH), 1634 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.16 (s, NH), 8.23 (d, 2H, *J* = 8.4 Hz), 8.07 (d, 2H, *J* = 7.5 Hz), 7.95 (d, 2H, *J* = 7.9 Hz), 7.61-7.66 (m, 4H), 7.56 (t, 2H, *J* = 7.1 Hz), 7.49 (t, 2H, *J* = 7.9 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 134.33, 133.71, 128.42, 125.87, 125.68, 122.86, 121.34, 117.42; Mass (EI): m/z = 314 $(M+2)^+$.

2.1.11 N, N′-*bis*(2-trifluoromethylphenyl) urea (**3k**): White solid; Melting Point: 241-42 °C; Mass (EI): m/z = 292 $[M]^+$.



Scheme 1. Synthesis of diarylureas

Table 1. Physical and spectroscopic data of N, N'-diarylureas (3a-k).

S.No	Ar	Time (min) & power	(%) Yield
3a		15 (450W)	62
3b		6 (450W)	61
3c		16 (450W)	60
3d		16 (450W)	62
3e		11 (450W)	69
3f		11 (450W)	70
3g		4 (360W)	56
3h		4 (360W)	42
3i		7 (360W)	60
3j		3 (360W)	63
3k		5(360W)	56

3. RESULTS AND DISCUSSION

All the synthesized compounds 3a-k has been characterized by IR, ^{1}H NMR and mass spectral data. Some of the compounds are characterized by single crystal X-ray diffraction studies [15]. The compound N, N'-*bis*(3-chlorophenyl)urea (3b) has been taken as representative example and its spectral data assignments are discussed below.

Spectral characterization of N, N'-*bis* (3-chlorophenyl)urea (3b)

The IR spectrum of compound 3b (Figure 2) shows characteristic carbonyl absorption frequency at 1635 cm^{-1}, NH stretching frequency at 3291 cm^{-1} and C-Cl stretching frequency at 872 cm^{-1}.

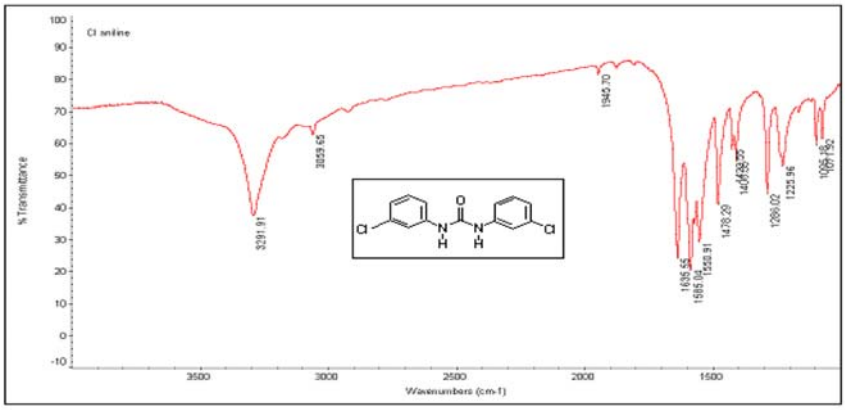


Figure 1. IR spectrum of N, N'-*bis*(3-chlorophenyl)urea **(3b)**.

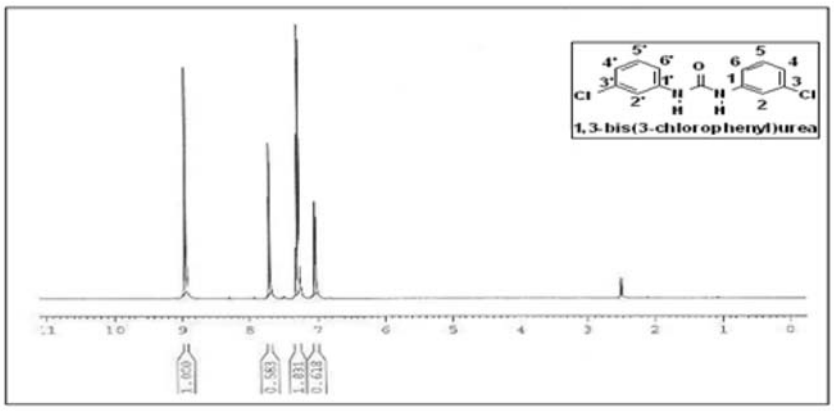


Figure 2. ^{1}H NMR of N, N'-*bis*(3-chlorophenyl)urea (3b).

The ^{1}H NMR spectrum of compound 3b (Figure 2) shows three sets of peaks equivalent to eight protons. The signal appearing at d 8.95 ppm is equivalent to two NH protons of 3b. The doublet at d 7.70 ppm is due to 2 and 2′ protons. As these protons are placed between two electron withdrawing groups, this signal appears at downfield compared to other aromatic protons. A multiplet between d 7.20-7.30 ppm equivalent to four protons is due to 4, 5, 4′ and 5′ protons of the symmetric aromatic rings. A double triplet at d 7.05 ppm is due to 6 and 62 protons, the signal of H-6 is split into doublet by the *ortho* proton with coupling constant

J = 7.2 Hz, each in turn got split into triplet by two *meta* protons H-4, H-2 with coupling constant J = 1.7 Hz, J = 2 Hz respectively. The IR, proton chemical shift values of the rest in this series have been assigned and are given in experimental section. EI mass spectrum of compound 3b (Figure 3) shows the parent ion peak at 281 $[M+1]^+$ and base peak at 194. The fragmentation of this compound has been shown in Figure 4. The formation of the desired compound has further been confirmed by single crystal X-ray diffraction studies of compound 3g [15].

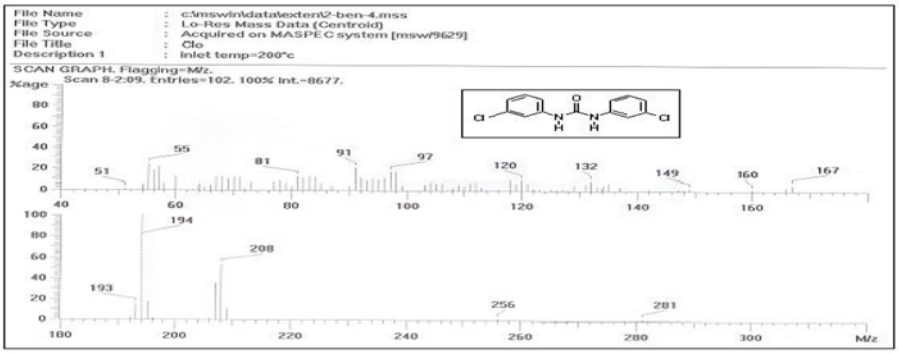


Figure 3. EI-MS spectrum of N, N′-*bis*(3-chlorophenyl)urea (3b).

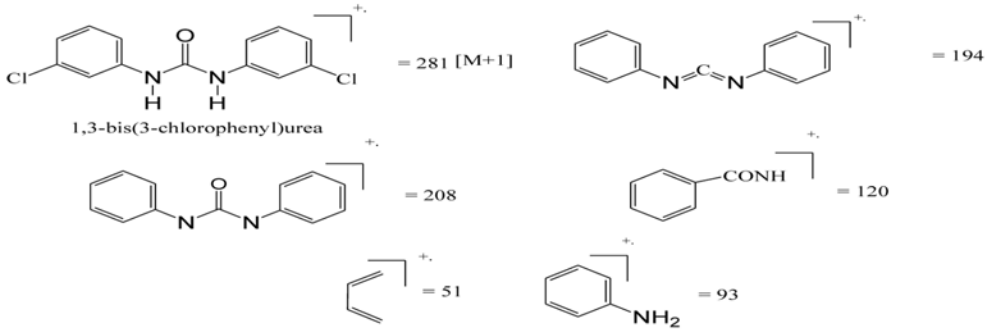


Figure 4. EI-Mass fragmentation of N, N′-*bis*(3-chlorophenyl)urea (3b).

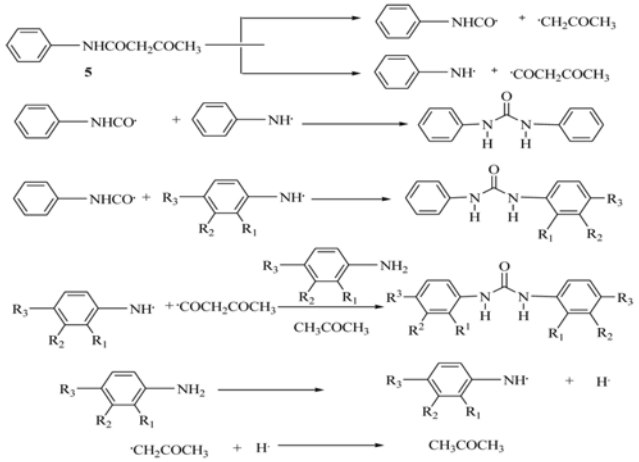
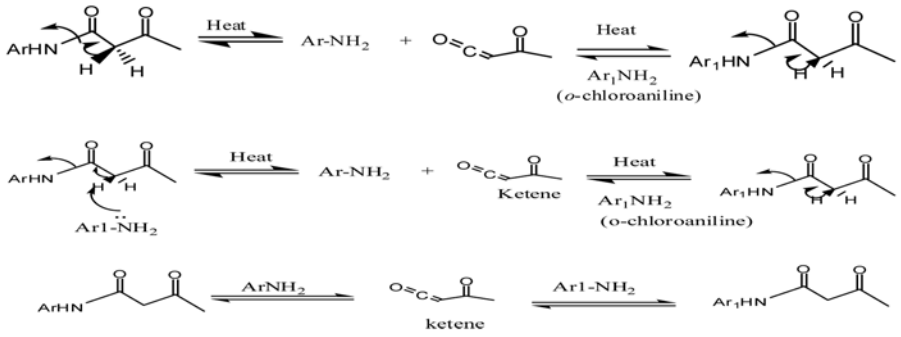


Figure 5. Mechanisms for the synthesis of diarylureas: i) Radical mechanism.

The synthesis of compounds 3a-k is attributed to the initial formation of acetoacetanilides followed by their subsequent reactions with a second molecule of arylamine to give diarylureas and acetone (Scheme 2; i) Radical mechanism). The proposed mechanisms were proved by the formation of unsymmetrical diarylureas from acetoacetanilide and aromatic amines. From the GC Mass spectrum of compound obtained in reaction with acetoacetanilide and *o-c*hloroaniline clearly indicates (Consolidated GC-MS data for the reaction mixture of acetoacteanilide and *o*-chloroaniline shown as Table 2) the formation of three compounds that is N, N′-diphenylurea, N-phenyl-N′-(4-chlorophenyl)urea and N, N′-*bis*(4-chlorophenyl) urea. It could be possible due to the formation of aryl amino free radical from acetoacetanilide and aromatic primary amines.

These free radicals react with the acetoacetanilide with the elimination of acetone. The carbonyl absorption frequency 1725 and 1660 cm^{-1} of acetoacetanilide is shifted to 1635 cm^{-1} in the diarylureas which is the characteristic absorption frequency of aromatic diamide. GC mass spectrum and IR are given in supplementary information (S1Figure 33-35). This reaction can also be explained by another possible thermal decomposition mechanism in which decomposition of acetoacetanilide may lead to formation of ketene and aryl amine. Then the arylamine will in turn react with ketene to form diarylurea (Scheme 2, ii) Thermal decomposition mechanism).



Scheme 2. Mechanisms of formation of diarylureas.

Table 2. Consolidated GC-MS data for the reaction mixture of acetoacetanilide and *o*-chloroaniline.

S. No	Name of the compound	Retention time	% composition	Mass
1.	N, N′-diphenylurea	1.52	51	211.1
2.	N-phenyl-N′ -(4-chlorophenyl)urea	1.70	41	245.2 (247.2)*
3.	N-phenyl-N′-(4-chlorophenyl)urea	1.8	6	279.1 (281.1)*

***Isotopic peak of chloride substituent.

4. ANTIMICROBIAL EVALUATION

4.1 Measurement of Minimum Inhibitory Concentration (MIC)

4.1.1 Media used

Muller Hinton broth and soboured dextrose broth from Himedia were used for anti bacterial activity screening and anti fungal activity screening respectively. All the culture was sterilized by autoclaving at 15 lbs for 20 min.

4.1.2 Broth dilution method

Exactly 1mg/ml stock solution of the synthesized compounds were made using DMSO as a solvent. From these stock solutions required quantities of drugs solutions were mixed with the known quantities of the sterile broth aseptically to provide the following concentration 100, 150, 200, 250, 300, 350, 400, 450, 500, 550 and 600 µg /ml. About 1ml of the media containing the drug was dispensed into each sterile test tube. 1 µL of standardized microorganisms (1×10^5 CPU/ml) was inoculated into the test tubes aseptically. After inoculation all the tubes were incubated at 37±1 °C for 24h, then the tubes were observed for the growth of microorganisms using optical density measurement method. The lowest concentration of the synthesized compounds inhibiting the growth of the given bacteria was considered as min inhibitory concentration of the test compounds against those bacteria. The MIC values of each compound against various in *Pseudomonas aeruginosa* ATCC-27853, *Proteus mirabilis* ATCC-19181, *Staphylococcus aureus* ATCC-700699, *Klebsiella pneumonia* ATCC-10273, *Staphylococcus typhi* ATCC-700931 and *Entrococci* Clinical sample.

4.1.3 Antibacterial and antifungal screening (well diffusion method)

A suspension of *S. aureus* was added to the sterile *Muller Hinton* agar medium at 45 °C in aseptic environment. The mixture was transferred to sterile Petri dishes and allowed to solidify. Wells of 6mm in diameter were made using well-borer, Specified concentration of synthesized compounds and the standard were applied on the surface of agar plates. DMSO was used as control. All the plates were left for 1h-4h as a period of pre incubation diffusion to minimize the effects of variation in time between the applications of the different solutions. Then the plates were incubated at 37±1 °C for 18 -24 h and were observed for antibacterial activity. The diameter of the zone of inhibition was measured for the plates in which the zone of inhibition was observed, the process was triplicated and average zone of inhibitions were calculated

(Table 4-6). A similar procedure was carried out for studying the antibacterial activity of compounds (3a-k) against *Gram negative* organisms such as *Pseudomonas aeruginosa, Salmonella typhi, Klebsiella pneumonia, proteous mirabilis* and *Gram positive Staphylococcus aureus*. The measured zone of inhibition in mm and the MIC values are given in Table 3.

Table 3. MIC values of diarylureas (3a-k).

S. No	MIC values µg and Name of the organism					
	P. aeruginosa	*S. typhi*	*K. pneumonia*	*P. mirabilis*	*S. aureus*	*E. cocci*
3a	100	140	150	130	170	140
3b	100	140	150	130	170	140
3c	200	230	200	230	240	240
3d	200	230	240	230	220	240
3e	100	130	150	130	170	120
3f	120	110	150	130	180	130
3g	100	110	130	130	120	140
3h	110	120	120	130	100	130
3i	110	130	120	130	160	130
3j	160	130	150	130	170	140
3k	100	130	100	130	150	120

Table 4. Antibacterial activities of diraylureas (3a-k) (zone of inhibition in mm).

S.No	Name of the organisms											
	P. aeruginosa (ATCC27853)				*S. typhi (ATCC70099)*				*K. pneumonia (ATCC-10273)*			
	100 µg/mL	150 µg/mL	200 µg/mL	Std*	100 µg/mL	150 µg/mL	200 µg/mL	Std*	100 µg/mL	150 µg/mL	200 µg/mL	Std*
3a	8	8	8	30	8	12	15	34	6	7	13	36
3b	6	9	11	30	6	9	11	34	7	12	14	36
3c	8	11	14	30	7	11	12	34	5	8	10	36
3d	9	11	15	30	6	8	10	34	5	9	11	36
3e	8	10	12	30	7	9	12	34	7	11	14	36
3f	8	10	12	30	8	10	15	34	7	10	18	36
3g	12	14	18	30	8	12	17	34	8	13	17	36
3h	13	15	20	30	7	13	18	34	8	12	20	36
3i	12	15	19	30	7	14	19	34	8	14	22	36
3j	11	13	19	30	8	16	20	34	9	14	20	36
3k	11	14	18	30	8	12	15	34	8	13	19	36

Table 5. Antibacterial activities of diraylureas (3a-k) (zone of inhibition in mm).

S.No	Name of the organisms											
	P. mirabilis ATCC-19181				*S. aureus* ATCC-700699				*Entrococci* Clinical sample			
	100 µg/mL	150 µg/mL	200 µg/mL	Std*	100 µg/mL	150 µg/mL	200 µg/mL	Std*	100 µg/mL	150 µg/mL	200 µg/mL	Std*
3a	9	11	18	30	-	-	5	24	7	13	17	35
3b	8	12	15	30	5	12	19	24	10	16	18	35
3c	7	12	14	30	-	-	-	24	10	18	19	35
3d	-	-	-	30	-	-	-	24	11	15	20	35
3e	-	-	-	30	5	7	10	24	12	16	23	35
3f	-	-	-	30	6	9	13	24	10	16	23	35
3g	8	8	10	30	5	9	12	24	11	15	20	35
3h	11	15	23	30	7	10	14	24	12	16	23	35
3i	10	11	14	30	7	12	14	24	11	15	23	35
3j	7	8	13	30	9	11	15	24	12	14	19	35
3k	12	15	24	30	8	11	14	24	12	14	23	35

Table 6. Antifungal activities of diarylureas (3a-k) (zone of inhibition in mm).

S.No	Name of the organisms											
	Candida albicans				*Aspergillus niger*				*Aspergillus flavus*			
	100 µg/mL	200 µg/mL	300 µg/mL	Std*	100 µg/mL	200 µg/mL	300 µg/mL	Std*	100 µg/mL	200 µg/mL	300 µg/mL	Std*
3a	6	8	10	24	8	9	10	24	6	7	9	21
3b	8	9	12	24	-	-	-	24	7	8	10	21
3c	6	9	11	24	-	-	6	24	-	-	-	21
3d	9	12	13	24	9	11	12	24	-	-	-	21
3e	7	11	15	24	-	-	-	24	-	-	-	21
3f	8	11	17	24	7	9	14	24	7	9	14	21
3g	11	15	20	24	11	13	16	24	12	15	17	21
3h	10	13	16	24	12	15	17	24	11	14	15	21
3i	12	15	18	24	11	14	16	24	12	14	16	21
3j	10	12	15	24	10	11	13	24	9	13	15	21
3k	12	13	18	24	11	14	15	24	10	12	16	21

5. CONCLUSION

In the present work the synthesis of diaryl ureas were attempted successfully without phosgene, cyanate or isocyanate intermediate. The synthesized compounds were subjected to anti microbial studies. The zone of inhibition values inferred that 3g, 3h, 3i, 3j were show good activity against *Pseudomonas aeruginosa* and *Salmonella typhi* and moderate activity towards *Klebsiella pneumonia.* 3b, 3f, 3g-j were shown to have moderate activity against *Staphylococcus aureus*. 3b, 3k, 3h,

3i show activity against *Proteus mirabilis* 3a-g are have lesser activity towards all the bacteria screened. Compounds like 3a, 3b and 3e are very less activity. The compounds 3h and 3k show comparable activity against Proteus mirabilis with respect to the standard ciprofloxacin. 3e, 3f, 3h and 3k are active against Entrococci. So the compounds 3h and 3k can be focused for further studies. (3a-k) were not shown promising antifungal activities.

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