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Microwave synthesis and antimicrobial activity of some N-aryl hydrazones

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Abstract

-N-arylhydrazone derivatives of N-phenyl anthranilic acid are pharmacologically active and are very useful. A number of hydrazide derivatives have been synthesized by the condensation of the hydrazide with the numbers of aromatic aldehydes and ketones in the presence of conc. hydrochloric acid as a catalyst. The reactions have been carried out under microwave irradiation. The structures of the products were confirmed by physico-chemical and spectral data like IR, NMR and Mass.

Key Words: N-phenyl anthranilic acid, hydrazone, hydrazide, microwave.

INTRODUCTION

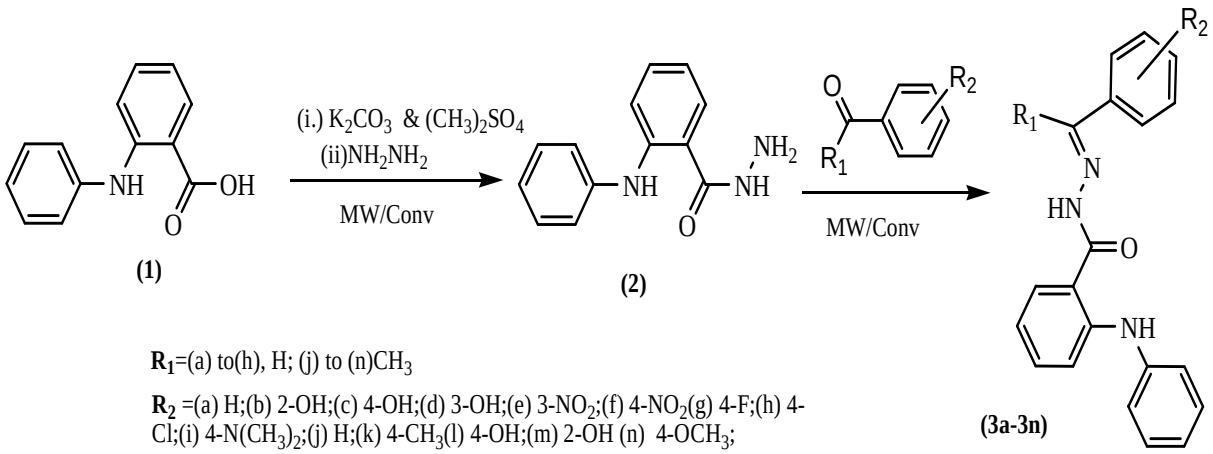
N-arylhydrazone derivatives play a vital role in biological fields**.** Hydrazide-hydrazones compounds are not only intermediate but they are also very effective organic compounds in their own right. Hydrazones have been demonstrated to possess, among other, antimicrobial, antimycobacterial, antidepressant, anticonvulsant, analgesic-anti-inflammatory, antimalarial, leishmanicidal, anticancer, and antiviral and vasodilator activities[1-11]. So in the present communication, some novel N-arylhydrazone derivatives of N-phenyl anthranilic acid were synthesized. The use of microwave irradiation[12-14 in chemical synthesis is eco-friendly and free from pollution hazard. The microwave-assisted reactions are rapid, safe, high yielding[15-16] and superior to conventional methods.

RESULTS AND DISCUSSION

The structures of the synthesized compounds were confirmed by their elemental and spectral analysis. The target compounds were obtained by the treatment of N-phenyl anthranilic acid with dimethyl sulphate in the presence of acetone (by conventional method) and potassium carbonate to give methyl 2-(phenyl amino) benzoate (1). The compound 1 on treatment with hydrazine hydrate gives 2-(phenylamino) benzohydrazide (2) in the presence of the catalytic amount of conc. hydrochloric acid. Finally the reaction of hydrazide with aromatic aldehydes / ketones yield different N-arylhydrazones, the target compounds **(Scheme 1)**. Under microwave irradiation, the synthesis of compounds was carried out in dimethyl formamide (DMF). It has been observed that under microwave irradiation, reactions were complete in few minutes with higher yields of final compounds. The synthesis of N-aryl hydrazones from N-phenyl anthranilic acid provides a fast, cheap and ecofriendly path.

All products were confirmed by IR spectral data showing characteristic two peaks in the range from 3423-3184 cm^{-1} indicating the presence of two –NH groups and sharp peak at 1515-1560 cm^{-1} indicated the presence of C=N group in the products. The ^{1}HNMR showed singlets in the range from δ 9.11-9.45 and 7.93-8.22 corresponding to –NH and –NH-N= proton, respectively in the products. A singlet at 6.14-6.22 ppm and 2.16-2.36 ppm in the ^{1}HNMR spectra of products indicated the presence of aldehydic (-N=CH-) and ketonic (-N=C-CH_3) protons respectively. The peak at 3.73 ppm (-NH_2 of hydrazide) was found to be absent in the spectra of products. The mass spectra of the products also confirmed the structure of the products.

Scheme1



R_1=(a) to(h), H; (j) to (n)CH_3

R_2 =(a) H;(b) 2-OH;(c) 4-OH;(d) 3-OH;(e) 3-NO_2;(f) 4-NO_2(g) 4-F;(h) 4-Cl;(i) 4-$N(CH_3)_2$;(j) H;(k) 4-CH_3(l) 4-OH;(m) 2-OH (n) 4-OCH_3;

It has been observed that the presence of fluoro, chloro or nitro groups in the moiety enhances its antibacterial activity. However, the degree of inhibition varied both with the test compound as well as with the bacterial species. Compounds 3a, 3d, 3e, 3f, 3g, 3h and 3k, show significant activity at 200 µg/mL concentration against, *S. aboni*, *S aureus* and *P. aeruginosa*, An examination of the data reveal that almost all the compounds showed mild to moderate antibacterial activity. The synthesized compounds donot reveled antifungal activity.

MATERIALS AND METHODS

All melting points were determined by open capillary tube method and are uncorrected. IR spectra were recorded (KBr) on FT-IR Unicorn Maltson 1000 spectrophotometer. ^{1}H-NMR spectra were recorded on Bruker Ac-80 (80 MHz) spectrometer in $CDCl_3$ using TMS as internal standard and chemical shifts are indicated in δ (ppm). Chemicals were purchased from commercial suppliers and were used without any further purification. The progress of the reaction was monitored on precoated silica gel 60 F254 plates (Merck) using different solvent systems. Mass spectra were recorded on Jeol D30 spectrophotometer. Elemental analyses for C, H and N were carried out using a Perkin -Elmer C, H, and N analyzer.

Synthesis of methyl 2-(phenyl amino) benzoate **(1)**
A mixture of N-phenyl anthranilic acid (0.01 mol), dimethyl sulphate (0.01 mol), a pinch of potassium carbonate and DMF (20.0 mL) was taken in Erlenmeyer flask fitted with a stemless funnel. The mixture was well stirred and irradiated in microwave oven for a period 2 min at 360 W (i.e. 30 % microwave power) with intermitted irradiation for 30 Sec. interval. The progress of the reaction was determined by TLC. The reaction mixture was allowed to cool and the filtrate was poured into the crushed ice. The crude product was crystallized from absolute alcohol (yield 84 %).

Elemental analysis (Found): C, 74.27; H, 5.56; N, 6.37; (Calculated): C, 73.99; H, 5.77; N, 6.16; Mol. Formula: $C_{14}H_{13}NO_2$; IR (cm^{-1}): 1720 (C=O), 3356 (NH), 2956 (Ar-CH); ^{1}H NMR (δ ppm): 6.56-7.80 (m, 9 H, Ar), 9.27 (s, 1H, NH), 3.56 (s, 3H, CH_3), MS: m/z $[M]^+$ 229.

Synthesis of 2-(phenyl amino) benzohydrazide **(2)**
A mixture of **1** (0.01 mol), 99 % hydrazine hydrate (0.02 mol) and ethanol (15.0 mL) were taken in Erlenmeyer flask and mixed thoroughly. Then the mixture was irradiated under microwave oven for 2.30 min at 240 W (i.e. 20 % microwave power) with intermitted irradiation for 30 sec. interval. Upon completion of the reaction (monitored by TLC), the reaction mixture was poured onto the crushed ice. The solid mass obtained was filtered and washed several times with water. The product was recrystallized with diethyl ether to give product 2. The physical data and R_f value are reported in Table-1.

Elemental analysis (Found): C, 78.47; H, 5.76; N, 18.84; (Calculated): C, 78.70; H, 5.77; N, 18.49: Mol. Formula: $C_{13}H_{13}N_3O$; IR (cm^{-1}): 1669 (C=O), 3423, 3325 (NH), 2956 (Ar-CH); ^{1}H NMR (δ, ppm): 6.46-7.70 (m, 9 H, Ar), 9.34 (s, 1H, NH), 8.14 (s, 1H, NH), 3.73 (s, 2H, NH_2); MS: m/z $[M]^+$ 227.

Synthesis of N-benzylidene-2- (phenylamino) benzohydrazide **(3a-3n)**
A mixture of 2-(phenyl amino) benzohydrazide (0.02 mol) and benzaldehyde (0.02 mol) in minimum amount of ethanol was taken in Erlenmeyer flask in the presence of two drops of conc. hydrochloric acid as a catalyst. Then the mixture was irradiated under microwave oven for 1 min at 240 W (i.e. 20 % microwave power) with intermitted irradiation for 15 sec .The progress of the reaction was determined by TLC. The reaction mixture was neutralized with a 10 % aqueous solution of sodium bicarbonate. The resulting precipitate was filtered, washed with water and

crystallized from ethanol. Compounds **3b-3n** were prepared similarly by using different arylaldehydes and arylketones.

N'-benzylidene-2- (phenylamino) benzohydrazide **(3a)**
Elemental analysis (Found): C, 76.47; H, 5.76; N, 13.67; (Calculated): C, 76.17; H, 5.43; N, 13.32; Mol. Formula: $C_{20}H_{17}N_3O$; IR (cm^{-1}): 1699 (C=O), 3423, 3325 (NH), 1515 (C=N), 2956 (Ar-CH); ^{1}H NMR (δ ppm): 6.77-7.74 (m, 14 H, Ar), 9.32 (s, 1H, HN), 8.18 (s, 1H, HN-N), 6.21 (s, 1H, N=CH); MS: m/z $[M]^+$ 315.

N'- (2-hydroxybenzylidene)-2-(phenylamino) benzohydrazide (**3b)**
Elemental analysis (Found): C, 72.19; H, 5.47; N, 13.08; (Calculated): C, 72.49; H, 5.17; N, 12.68; Mol. Formula: $C_{20}H_{17}N_3O_2$; IR (cm^{-1}): 1691 (C=O), 3371, 3213 (NH), 1560 (C=N), 3548 (OH), 2929 (Ar-CH); ^{1}H NMR (δ ppm): 6.71-7.62 (m, 13H, Ar), 9.45. (s, 1H, HN-), 8.20 (s, 1H, HN-N), 6.18 (s, 1H, N=CH); 5.22 (s, 1H, OH); MS: m/z $[M]^+$ 331.

N'- (4-hydroxybenzylidene)-2-(phenylamino) benzohydrazide (**3c)**
Elemental analysis (Found): C, 72.79; H, 5.40; N, 13.10; (Calculated): C, 72.49; H, 5.17; N, 12.68; Mol. Formula: $C_{20}H_{17}N_3O_2$; IR (cm^{-1}): 1693 (C=O), 3315, 3267 (NH), 1552 (C=N), 3465 (OH), 2939 (Ar-CH); ^{1}H NMR (δ ppm): 6.72-7.82 (m, 13H, Ar), 9.30 (s, 1H, HN-), 8.22 (s, 1H, HN-N), 6.20 (s, 1H, N=CH);, 5.14 (s, 1H,OH); MS: m/z $[M]^+$ 331.

N'- (3-hydroxybenzylidene)-2-(phenylamino) benzohydrazide **(3d)**
Elemental analysis (Found): C, 72.69; H, 4.88; N, 13.05; (Calculated): C, 72.49; H, 5.17; N, 12.68; Mol. Formula: $C_{20}H_{17}N_3O_2$; IR (cm^{-1}): 1701 (C=O), 3301, 3195 (NH), 1546 (C=N), 3469 (OH), 3031 (Ar-CH); ^{1}H NMR (δ, ppm): 6.78-7.52 (m, 13H, Ar), 9.28, (s, 1H, HN-), 8.18 (s, 1H,HN-N), 6.14 (s, 1H, N=CH); 5.18 (s, 1H, OH); MS: m/z $[M]^+$ 331.

N'- (3-nitrobenzylidene)-2-(phenylamino) benzohydrazide **(3e)**
Elemental analysis (Found): C, 66.47; H, 4.76; N, 15.87; (Calculated): C, 66.66; H, 4.48; N, 15.55; Mol. Formula: $C_{20}H_{16}N_4O_3$; IR (cm^{-1}): 1699 (C=O), 3420, 3308 (NH), 1525 (C=N), 2936 (Ar-CH); ^{1}H NMR (δ, ppm): 6.85-8.30 (m, 13 H, Ar), 9.43 (s, 1H, HN), 8.20 (s, 1H, HN-N), 6.16 (s, 1H, N=CH); MS: m/z $[M]^+$ 360.

N'- (4-nitrobenzylidene)-2-(phenylamino) benzohydrazide **(3f)**
Elemental analysis (Found): C, 66.37; H, 4.26; N, 15.25; (Calculated): C, 66.66; H, 4.48; N, 15.55; Mol. Formula: $C_{20}H_{16}N_4O_3$; IR (cm^{-1}): 1705 (C=O), 3325, 3218 (NH), 1515 (C=N), 2930 (Ar-CH); ^{1}H NMR (δ, ppm): 6.87-8.22 (m, 13 H, Ar), 9.21 (s, 1H, HN), 8.22 (s, 1H, HN-N), 6.14 (s, 1H, N=CH); MS: m/z $[M]^+$ 360.

N'- (4-fluorobenzylidene)-2-(phenylamino) benzohydrazide **(3g)**
Elemental analysis (Found): C, 75.67; H, 4.56; N, 12.35; F, 6.05 (Calculated); C, 72.06; H, 4.84; N, 12.61; F, 5.70; Mol. Formula: $C_{20}H_{16}FN_3O$; IR (cm^{-1}): 1699 (C=O), 3323, 3225 (NH), 1515 (C=N), 2956 (Ar-CH) 786 (C-F); ^{1}H NMR (δ ppm): 6.77-7.74 (m, 13 H, Ar), 9.11 (s, 1H, HN), 8.06 (s, 1H, HN-N), 6.18 (s, 1H, N=CH);; MS: m/z $[M]^+$ 333.

Table 1: The physico-chemical data of synthesized compounds (3a-3n)

Compound	R_1, R_2	M. Wt	Microwave Method		m.p (°C)	R_f
			Yield (%)	Reaction time (min)		
1	- -	229	85	1.00	181	0.68
2	- -	227	88	2.30	153	0.67
3a	R_1= R_2 =H	315	89	1.00	218	0.71
3b	R_1= H, R_2 =2-OH	331	90	1.30	161	0.69
3c	R_1= H, R_2=4OH	331	91	0.30	238	0.70
3d	R_1=H, R_2=3-OH	331	92	0.30	208	0.68
3e	R_1= H, R_2=3-NO_2	360	89	0.45	179	0.65
3f	R_1 = H, R_2= 4-NO_2	360	88	0.30	244	0.67
3g	R_1=H, R_2=4-F	333	90	0.30	204	0.73
3h	R_1=H, R_2= 4-Cl	349	88	1.00	244	0.70
3i	R_1=H, R_2= 4-N $(CH_3)_2$	358	87	1.20	230	0.67
3j	R_1=CH_3, R_2=H	329	90	2.00	215	0.63
3k	R_1= CH_3, R_2= CH_3,	343	87	1.00	222	0.64
3l	R_1=CH_3, R_2 = 4-OH	345	86	2.00	206	0.68
3m	R_1=CH_3, R_2 = 2-OH	345	88	2.00	207	0.66
3n	R_1= CH_3, R_2=4-OCH_3	359	85	2.00	210	0.69

N'- (4-chlorobenzylidene)-2-(phenylamino) benzohydrazide **(3h)**
Elemental analysis (Found): C, 73.37; H, 6.46; N, 15.35; (Calculated); C, 73.72; H, 6.19; N, 15.63; Mol. Formula: $C_{20}H_{16}ClN_3O$; IR (cm^{-1}): 1679 (C=O), 3328, 3234 (NH), 1532 (C=N), 736 (C-Cl), 2923 (Ar-CH); ^{1}H NMR (δ ppm): 6.77-7.78 (m, 13H, Ar), 9.20 (s, 1H, HN) 8.11 (s, 1H, HN-N), 6.22 (s, 1H, N=CH); MS: m/z $[M]^+$ 349.

N'- (4-(dimethylamino) benzylidene)-2-(phenylamino) benzohydrazide **(3i)**
Elemental analysis (Found): C, 68.37; H, 4.46; N, 12.35; Cl, 10.25 (Calculated); C, 68.67; H, 4.61; Cl, 10.13; N, 12.01; Mol. Formula: $C_{22}H_{22}N_4O$; IR (cm^{-1}): 1699 (C=O), 3359, 3184 (NH), 1540 (C=N), 1363 (N $(CH_3)_2$), 3037 (Ar-CH); ^{1}H NMR (δ ppm): 6.96-7.70 (m, 13H, Ar), 9.12 (S, 1H, HN), 8.08 (s, 1H, HN-N), 6.20 (s, 1H, N=CH) 2.92 [m,6H, N-$(CH_3)_2$]; MS: m/z $[M]^+$ 358.

2-(phenylamino)-N'- (1-phenylethylidene) benzohydrazide **(3j)**
Elemental analysis (Found): C, 76.37; H, 6.16; N, 12.45; (Calculated); C, 76.57; H, 5.81; N, 12.76; Mol. Formula: $C_{21}H_{19}N_3O$; IR (cm^{-1}): 1676 (C=O), 3366,3224 (NH), 1533 (C=N), 2971 (Ar-CH), 2864 (CH_3); ^{1}H NMR (δ ppm): 6.82-7.60 (m, 14H, Ar), 8.98 (s 1H, HN), 7.93 (s, 1H, HN-N), 2.32 (s, 3H, N=C-CH_3); MS: m/z $[M]^+$ 329.

2-(phenylamino)-N'- (1-p-tolylethylidene) benzohydrazide **(3k)**
Elemental analysis (Found): C, 76.58; H, 6.36; N, 11.90; (Calculated); C, 76.94; H, 6.16; N, 12.24; Mol. Formula: $C_{22}H_{21}N_3O$; IR (cm^{-1}): 1686 (C=O), 3356,3218 (NH), 1543 (C=N), 2971 (Ar-CH), 2854 (CH_3); ^{1}H NMR (δ, ppm): 6.46-7.70 (m, 13H, Ar), 9.13 (s, 1H, HN), 8.14 (s 1H, HN-N), 2.70 (s,3H,CH_3), 2.36 (s, 3H, N=C-CH_3) ; MS: m/z $[M]^+$ 343.

N'- (1-(4-hydroxyphenyl) ethylidene)-2-(phenylamino) benzohydrazide (**3l**)
Elemental analysis (Found): C, 73.40; H, 5.36; N, 11.90; (Calculated); C, 73.03; H, 5.54; N, 12.17; Mol. Formula: $C_{21}H_{19}N_3O_2$; IR (cm-^{1}): 1705 (C=O), 3350,3224 (NH), 1548 (C=N), 2981 (Ar-CH), 2834 (CH_3); ^{1}H NMR (δ, ppm): 6.62-7.70 (m, 13H, Ar), 9.23 (s 1H, HN), 8.18 (s, 1H, NH-N), 4.90 (s, 1H, OH) 2.28 (s, 3H, N=C-CH_3); ; MS: m/z $[M]^+$ 345.

N'- (1-(2-hydroxyphenyl) ethylidene)-2-(phenylamino) benzohydrazide **(3m)**
Elemental analysis (Found): C, 73.35; H, 5.30; N, 12.20; (Calculated); C, 73.03; H, 5.54; N, 12.17; Mol. Formula: $C_{21}H_{19}N_3O_2$; IR (cm-^{1}): 1715 (C=O), 3355,3220 (NH), 1540 (C=N), 2989(Ar-CH), 2830 (CH_3); ^{1}H NMR (δ, ppm): 6.70-7.80 (m, 13H, Ar), 9.26 (s 1H, HN), 8.12 (s, 1H, NH-N), 4.80 (s, 1H, OH), 2.22 (s, 3H, N=C-CH_3); MS: m/z $[M]^+$ 345.

N'- (1-(4-methoxyphenyl) ethylidene)-2-(phenylamino) benzohydrazide **(3n)**
Elemental analysis (Found): C, 73.35; H, 5.50; N, 12.00; (Calculated); C, 73.52; H, 5.89; N, 11.69; Mol. Formula: $C_{22}H_{21}N_3O_2$; IR (cm-^{1}): 1690 (C=O), 3348,3218 (NH), 1547 (C=N), 2980(Ar-CH), 2828 (CH_3) ^{1}H NMR (δ, ppm): 6.60-7.50 (m, 13H, Ar), 9.08 (s 1H, HN), 8.16 (s, 1H, HN-N), 3.91 (s, 3H, OCH_3), 2.16 (s, 3H, N=C-CH_3); MS: m/z $[M]^+$ 359.

Antimicrobial Study
All the synthesized compounds were tested for their antimicrobial activity against four bacterial [*S. aboni (*MTCC 38858), *S. aureus* (MTCC 737), *P. aeruginosa*, *(*MTCC 1688), *E.coli* (MTCC 1687) and one fungal strain *C. albicans* (MTCC 207) at a concentration of 100 µg/mL using cup plate agar disk diffusion method.[17] Ciprofloxacin and Fluconazole were used as standards for antibacterial and antifungal activity, respectively. The dimethylsulfoxide (DMSO) was used as a control for all the type of microorganisms. The control showed no activity against the strains of microorganisms. The minimum inhibitory concentration (MIC) was determined using tube dilution method[18] according to the standard procedure.

Disk diffusion method
Mueller-Hinton agar was used as the growth medium for the bacterial strains and Sabouraud agar was as growth medium for fungal species. The petridishes used for antibacterial screening were incubated at 37 ±1°C for 24 h, while those for antifungal activity were incubated at 28 ±1°C for 48-72 h. Antibacterial activity and antifungal activity was measured as a function of diameter of zone of inhibition (mm). The results were compared with standard drugs, Ciprofloxacin for antibacterial activity and Fluconazole for antifungal activity. The observed zone of inhibition at various concentrations for all the synthesized compounds is presented in Table 2. All the synthesized compounds showed mild to moderate activity against all the bacterial strains whereas none of the compounds showed significant activity against the fungal strain *Candida albicans.*

Minimal inhibitory concentration
Meuller Hinton broth was used as a culture Medium. Sterilized medium was dispensed in each borosilicate glass test tube. The drug solution was added in order to attain final drug concentrations of 400,200, 100, 50, 25, and 12.5, µg/mL. Inoculums of standard suspension (0.1 mL of the test organism strain which contains 106 bacilli/mL) were added. The tubes were incubated at 37ºC for 48 hr and then examined for the presence or absence of growth of the

organism. The lowest concentration, which showed no visible growth, was taken as an end point minimum inhibitory concentration (MIC). The testing results are given in Table 2. The antifungal activity of compounds has been assayed in vitro at a concentration of 200 µg/mL and 100 µg/mL against *Candida albicans*, which were maintained on nutrient agar slants, which were stored at 4ºC. none of the synthesized compounds was found to possess better activity than fluconazole.

Table 2: *In-vitro* antimicrobial activity of compounds (3a-3n)

Zone of Inhibition in mm (MIC in µg/mL)					
Compounds	***S.aboni* (MTCC 3858)**	***S.aureus* (MTCC 737)**	***P. aeriginosa* (MTCC 1688)**	***E.Coli* (MTCC 1687)**	***C. albicans* (MTCC 207)**
3a	22.10(400>)	19.20(<400)	22.00(400<)	19.00(>400)	(>400)
3b	22.20(400>)	18.80(<400)	22.00(400<)	18.90(>400)	(>400)
3c	23.00(400>)	18.60(<400)	23.00(400>)	18.50(>400)	(>400)
3d	23.00(400>)	18.10(<400)	20.00(>400<)	18.10(>400)	(>400)
3e	26.00(200<)	22.00(400<)	21.00(200)	19.10(>400)	(>400)
3f	25.00(200>)	18.10(<400)	20.00(200<)	18.10(>400)	(>400)
3g	28.10(200)	26.20(200<)	23.00(400)	18.80(>400)	(>400)
3h	28.10(200)	26.60(200)	20.60(>400)	19.50(>400)	(>400)
3i	22.10(400>)	18.20(<400)	22.00(400<)	18.00(>400)	(>400)
3j	22.00(400>)	18.50(<400)	21.00(400<)	18.90(>400)	(>400)
3k	22.75(400>)	18.20(<400)	22.60(400<)	18.10(>400)	(>400)
3l	22.40(400>)	18.60(<400)	16.20 (>400)	17.20(>400)	(>400)
3m	21.50(400>)	17.20(<400)	18.40(<400)	17.40(>400)	(>400)
3n	22.20(400>)	21.20(400>)	18.20(>400)	16.20(>400)	(>400)
Ciprofloxacin	35.42(0.2)	31.11(0.4)	30.45(0.4)	31.34(0.1)	(>400)
Fluconazole	-	-	-	-	30.15(6.0)

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