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Paper

Syntheses of 1,5-benzothiazepines: Part XXXIII- Syntheses and antimicrobial studies of 10-substituted-6-(4-methoxyphenyl)-6*H*-6*a*,7-dihydro-7-(4-methoxyphenyl/3,4-dimethoxyphenyl)[1]benzopyrano-[3,4-*c*][1,5]benzothiazepines

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Two flavindogenides, 2-(4-methoxyphenyl)-3-(4-methoxybenzylidene)-flavanone, **8a** and 2-(4-methoxyphenyl)-3-(3,4-dimethoxybenzylidene)-flavanone **8b**, are reacted with 5-substituted-2-aminobenzenethiols **3a-f** (the substituents being halogens, fluoro, chloro or bromo, methyl and alkoxyls, methoxyl or ethoxyl), to give respective 12 new compounds, 10-substituted-6-(4-methoxyphenyl)-6*H*-6*a*, 7-dihydro-7-(4-methoxyphenyl/3,4-dimethoxyphenyl)[1]benzopyrano[3,4-*c*]-[1,5]benzothiazepines **10a-l** in 55-67% yields. The products are characterized on the basis of analytical and spectral data. The synthesized compounds are screened for antimicrobial activity against the bacteria *Staphylococcus aureus, Pseudomonas aeruginosa,* and the fungus *Candida albicans*. All the methoxy-substituted benzopyranobenzothiazepines have showed moderate to comparable activity (using gatifloxin, natilmicin as reference standard) against the gram-positive bacteria *S. aureus* and the gram-negative bacteria *P. aeruginosa.* They have also showed significant antifungal activity (compared to fluconazole) against *C. albicans*, the maximum activity being that of the compound **10k** having maximum methoxyl groups, while the fluoro compounds **10a** and **10g** are completely inactive.

Keywords: Benzopyranobenzothiazepines, zimet, antimicrobial activity

Immense chemotherapeutic applications[1-5] of diltiazem, a compound having 1,5-benzothiazepine nucleus with 4-methoxyphenyl group at position 2, acetyloxy at 3, oxo at 4 and dimethylaminoethyl group at 5 interested the chemists to look for more improved CVS drugs. Introduction of chlorine at position 8 in diltiazem and replacement of one methyl group by an isopropyl group at position 5 yielded further improved CVS drugs, clentiazem[6,7] and siratiazem[8,9] respectively, which have been designated by WHO as second generation drugs, the first being diltiazem. All these bicyclic heterocyclic drugs possess a 4-methoxyphenyl group. The heterocyclic benzopyrano-1,5-benzodiazepine drug, patented as zimet, having 1,5-benzodiazepine ring fused with benzopyran ring, has methoxyl groups at positions 3 and 4. This compound has been reported to possess[10] antineoplastic activity against dreadful diseases like leukemia, melanoma B_{16}, Lewis lung carcinoma, tumour *etc*. Tetracyclic benzopyranobenzothiazepines, analogous to benzopyranobenzodiazepines, have been reported to show cardiovascular activity like antiarrhythmic[11], antiischemic[12], antihypertensive[13], coronary vasodilating[14] etc.

It was, therefore, thought to synthesize a series of tetracyclic benzopyranobenzothiazepines having varying substituents like halogens[15-17], hydroxyl[18], alkoxyl groups[19, 20] *etc*. A series of benzopyranobenzothiazepines having 4-flourophenyl group at position 7 were found to possess[16] moderate to good antimicrobial activity. Benzopyranobenzothiazepines with monochloro and dichlorophenyl group at position 7 also showed[17] similar antimicrobial activity. In the series of compounds having halogens (like F, Cl, Br), methyl and alkoxyls (methoxyl and ethoxyl) in the fused benzene ring of benzothiazepine moiety of benzopyranobenzothiazepines having an alkoxyphenyl group (ethoxyphenyl[20] or methoxyphenyl[19]) at position 7, showed cardiovascular and antimicrobial activity. Interestingly, the substituted benzopyranoben-

zothiazepines having methoxyphenyl group were found to possess[19] mild analgesic and anticonvulsant activity, whereas those with ethoxyphenyl group, were found to exhibit[20] useful antifungal and antibacterial activity. These studies have led us to synthesize a further series of benzopyranobenzothiazepines having methoxyl groups (4-methoxyphenyl or 3,4-dimethoxyphenyl) and study their antimicrobial activity. The results are reported in the present communication.

Results and Discussion

To attain the objective of having a series of benzopyranobenzothiazepines having F, Cl, Br, CH_3, OCH_3, OC_2H_5 in the fused benzene ring of benzothiazepine moiety, 2-aminobenzenethiols having these substituents at position 5 were prepared starting from *p*-substituted anilines **1a-f**, carrying out their thiocynation to obtain the respective 6-substituted-2-aminobenzothiazoles **2a-f**, which on hydrolysis afforded the first precursors, 5-substituted-2-aminobenzenethiols **3a-f**. The second precursors, two arylidene flavanones, 2-(4-methoxyphenyl)-3-(4-methoxybenzylidene)-flavanone **8a** and 2-(4-methoxyphenyl)-3-(3,4-dimethoxybenzylidene)-flavanone **8b**, having exocyclic unsaturation in conjugation with the carbonyl group, were obtained by the reaction of flavanone, **6** with 4-methoxybenzaldehyde **7a** and 3,4-dimethoxybenzaldehyde **7b**, respectively as it has been established[15-23] that compounds having α,β-unsaturated carbonyl system react with 5-substituted-2-aminobenzenethiols. The flavanone, in turn, was obtained by the reaction of *o*-hydroxyacetophenone **4** with *p*-methoxybenzaldehyde **5** (**Scheme I**).

Equimolar quantities of 5-substituted-2-aminobenzenethiols **3a-f** were reacted with flavindogenides, **8a** and **8b** in dry ethanol containing trifluoroacetic acid as catalyst by refluxing for 3 to 4 hr. The completion of the reaction was ascertained by TLC monitoring. The solvent was removed under reduced pressure and the crude thus obtained was crystallized from ethanol, the purity being ascertained by TLC. The final products were characterized on the basis of elemental and spectral analysis (**Tables I** and **II**).

The acid catalyzed mechanism[15-23] of the reaction between the substituted arylidene flavanones **8a** and **8b** with 5-substituted-2-aminobenzenethiols **3a-f**, is understood to take place by the protonation of the carbonyl group of arylidene flavanones, which renders the methine carbon electrophilic and thus prone to nucleophilic attack by sulfhydryl electrons. The Michael intermediates, **9a-l** undergo dehydrative cyclization, to give the final products **10a-l** (**Scheme II**).

The IR spectra of the products indicated the completion of reactions as the characteristic absorptions in the range 1700-1640 cm^{-1} for the C=O function and the NH_2 absorption at 3400-3100 cm^{-1} were absent. The presence of a strong absorption signal in the range 1612-1602 cm^{-1} is characteristic of C=N (ref. 24).

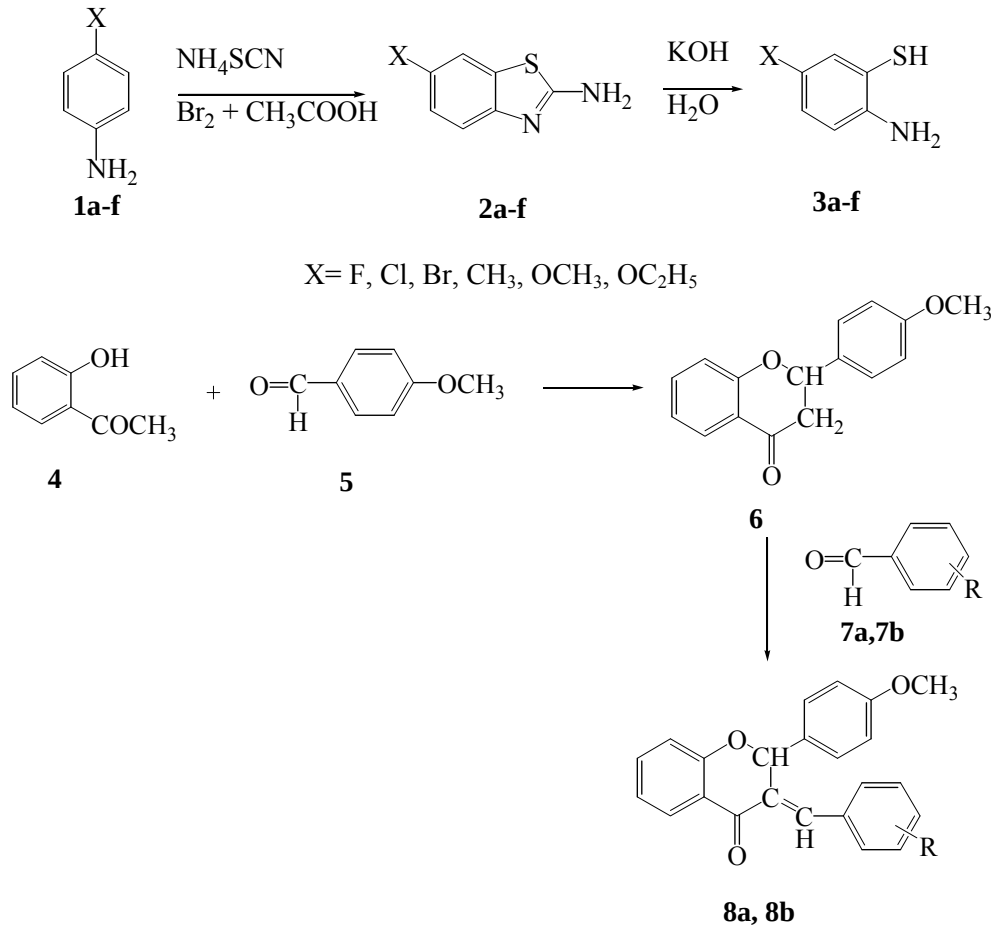
The ^1H NMR spectra of compounds **10a-f** showed two prominent three proton peaks near δ 3.36 and 3.40 while compounds **10g-l** showed three proton absorption peaks near δ 3.70, 3.80 and 3.90 corresponding to three methoxyl groups. The spectra also showed a double-doublet of one proton at δ 3.64-3.72 (J_1=12.3, J_2=1.2) assignable to C_{6a}-H and two doublets at δ 4.90-4.93 (J=1.2 Hz) and δ 4.96-5.07 (J=12.2 Hz), integrating for one proton each that may be assigned to C_6-H and C_7-H respectively. The downfield absorptions of the last two protons are due to their attachment to oxygen and sulfur atoms, respectively. Aromatic protons are found to show multiplets in the downfield region of the spectra, i.e. at δ 6.02-8.47 (**Table II**).

In ^{13}C NMR spectral studies, absorptions in the range, δ 55.5-56.1 may be assigned to methoxy carbons. The absorption signals observed at around δ 76.6, 46.3 and 66.4 may be assigned to carbons, C-6, C-6*a* and C-7 respectively. Aromatic carbons of the molecules were observed at around δ 118, 120, 121, 124, 125, 126, 127, 128, 129, 131, 131, 133, 135, 136, 136, 137, 137, 137, 138, 142, 151, 155 and 161.

In ^{19}F NMR of compounds **10a** and **10g**, the absorption at δ –110.00 and –110.25 respectively is assigned due to fluorine.

The mass spectra of compounds **10b** and **10h** showed that the intensity of $[M+2]^+$ peaks were nearly one third of intensity of M^+ peak, indicating the presence of chlorine atom in the molecule, while in compounds **10c** and **10i**, the intensity of $[M+2]^+$ peak and M^+ peak were found to be nearly equal, confirming the presence of bromine atom. In other compounds, molecular ion peaks M^+ and $[M+2]^+$ corresponded to the calculated molecular mass of the compounds. The results of elemental analysis were found to be satisfactory as in **Table I**.

Antimicrobial activity. All the synthesized compounds **10a-l** were evaluated for their relative anti-



Compd	R
7a, **8a**	4-OCH_3
7b, **8b**	3,4-$(OCH_3)_2$

Scheme I

Table I — Physical constants and micro-analytical data of compounds **10a-l**

Compd	X	m.p. (°C)	R_f	Yield (%)	Mol. formula (Mol. mass)	Found (Calcd) (%)		
						C	H	N
10a	F	126-27	0.73	60	$C_{30}H_{24}NO_3SF$ (497)	72.90 (72.43	4.66 4.83	2.79 2.82)
10b	Cl	122-23	0.68	62	$C_{30}H_{24}NO_3SCl$ (513.5)	- (-	- -	2.65 2.73)
10c	Br	116-17	0.71	59	$C_{30}H_{24}NO_3SBrF$ (558)	- (-	- -	2.37 2.51)
10d	CH_3	75-6	0.71	62	$C_{31}H_{27}NO_3S$ (493)	- (-	- -	2.72 2.83)
10e	OCH_3	130-31	0.69	65	$C_{31}H_{27}NO_4S$ (509)	73.29 (73.08	5.18 5.30	2.68 2.75)
10f	OC_2H_5	126-27	0.75	67	$C_{32}H_{29}NO_4S$ (523)	73.68 (73.42	5.39 5.54	2.82 2.68)

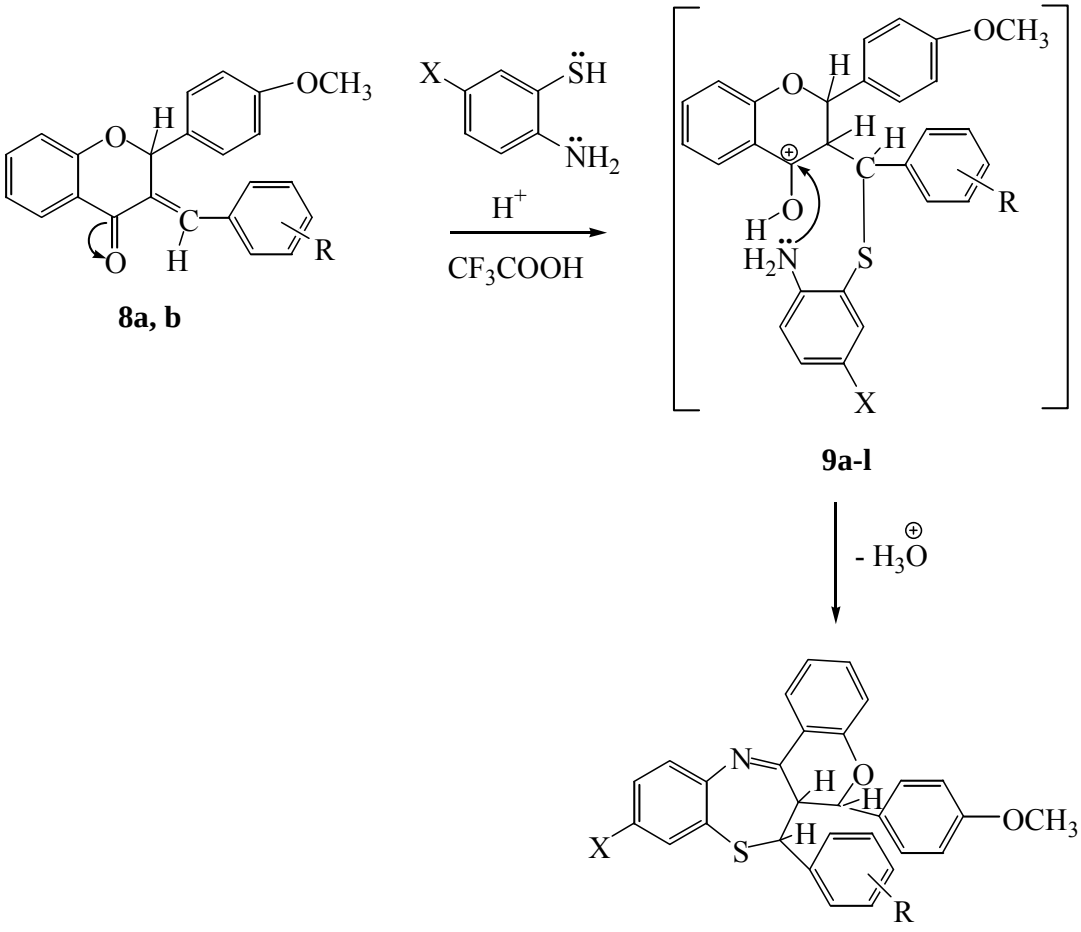
Contd.

Table I — Physical constants and micro-analytical data of compounds **10a-l**—*Contd.*

Compd	X	m.p. (°C)	R_f	Yield (%)	Mol. formula (Mol. mass)	Found (Calcd) (%)		
						C	H	N
10g	F	102-04	0.81	60	$C_{31}H_{26}NO_4SF$ (527)	70.24 (70.58	5.12 4.93	2.58 2.65)
10h	Cl	134-36	0.68	59	$C_{31}H_{26}NO_4SCl$ (543.5)	68.64 (68.44	5.68 5.97	2.42 2.57)
10i	Br	130-31	0.72	62	$C_{31}H_{26}NO_4SBr$ (588)	- (-	- -	2.42 2.38)
10j	CH_3	110-12	0.76	67	$C_{32}H_{29}NO_4S$ (523)	- (-	- -	2.62 2.67)
10k	OCH_3	110-13	0.78	60	$C_{32}H_{29}NO_5S$ (539)	- (-	- -	2.52 2.59)
10l	OC_2H_5	136-37	0.67	58	$C_{33}H_{31}NO_5S$ (553)	71.42 (71.60	5.82 5.60	2.57 2.53)

Table II — Spectral data of **10a-l**

Compd	X	Aromatic C-H	Aliphatic C-H	C-O-C	OCH_3 (s,3H)	C_{10}-XH	C_{6a}-H (dd, J_1=12.2, J_2=1.2)	C_7-H (d, J=12.2)	C_6-H (d, J=1.2)	Aromatic protons (m)
10a	F	3030	2960	1340	3.38,3.48	-	3.68	4.92	4.99	6.08-7.58
10b	Cl	2990	2945	1320	3.42,3.68	-	3.68	4.90	4.96	6.10-7.56
10c	Br	2995	2895	1294	3.14,3.46	-	3.64	4.90	4.96	6.05-7.50
10d	CH_3	3010	2930	1330	3.40,3.46	2.18 (s, 3H)	3.66	4.91	4.98	6.02-7.40
10e	OCH_3	3020	2890	1315	3.40,3.36	3.46 (s, 3H)	3.66	4.92	4.96	6.05-7.50
10f	OC_2H_5	3015	2898	1305	3.36,3.40	1.16 (t,3H,J=6) 4.03 (q,2H,J=6)	3.64	4.90	4.98	6.00-7.44
10g	F	3020	2962	1315	3.72,3.68, 3.70	-	3.64	4.91	5.07	6.72-8.24
10h	Cl	2990	2960	1310	3.98,3.90, 3.87	-	3.72	4.90	5.02	6.80-8.47
10i	Br	3010	2895	1320	3.71,3.74, 3.80	-	3.66	4.90	5.00	6.79-8.36
10j	CH_3	3020	2882	1310	3.92,3.87, 4.02	2.83 (s, 3H)	3.64	4.92	5.05	6.79-8.36
10k	OCH_3	3015	2960	1305	3.99,3.97, 4.01	3.98 (s,3H)	3.72	4.90	5.02	6.79-8.46
10l	OC_2H_5	3010	2898	1310	3.71,3.84, 3.91	1.17 (t,3H,J=6) 4.03 (q,2H,J=6)	3.64	4.92	5.02	6.80-8.44



8a, b

9a-l

10a-l

Compd	X	R	Compd	X	R
10a	F	4-OCH_3	**10g**	F	3,4-$(OCH_3)_2$
10b	Cl	4-OCH_3	**10h**	Cl	3,4-$(OCH_3)_2$
10c	Br	4-OCH_3	**10i**	Br	3,4-$(OCH_3)_2$
10d	CH_3	4-OCH_3	**10j**	CH_3	3,4-$(OCH_3)_2$
10e	OCH_3	4-OCH_3	**10k**	OCH_3	3,4-$(OCH_3)_2$
10f	OC_2H_5	4-OCH_3	**10l**	OC_2H_5	3,4-$(OCH_3)_2$

Scheme II

bacterial activity against the gram-positive bacteria, *Staphylococcus aureus* and the gram-negative bacteria *Pseudomonas aeruginosa,* and for antifungal activity against *Candida albicans* by using the filter paper disc method[25]. The results have been compared with those for the reference compounds gatifloxin and natilmicin for evaluating antibacterial activity and fluconazole for antifungal activity. Zones of inhibition, exhibited by the reference and test compounds were measured and relative activities were calculated as activity index (**Table III**). The zone of inhibition is the diameter of the area in which microorganisms have been destroyed.

$$\text{Activity index} = \frac{\text{Zone of inhibition exhibited by test compound}}{\text{Zone of inhibition exhibited by the reference compound}}$$

All the synthesized compounds **10a-l** were found to exhibit moderate to equal activity (activity index ≤1) against bacteria but showed significant activity (activity index >1) against fungus except the compounds **10a** and **10g**. Compounds **10a-f**, having 4-methoxyphenyl group at positions 6 and 7, were found to show better bactericidal activity, while compounds **10g-l**, having 4-methoxyphenyl at position 6 and 3,4-dimethoxyphenyl group at position 7, were found to exhibit better fungicidal activity. The compound **10k**, having maximum methoxy substituents, showed highest activity (activity index =1.85) against the fungus, but moderate activity against bacteria. This indicates that methoxy substituent plays an important role in antifungal activity but has not much role in bactericidal activity.

Experimental Section

All the melting points are uncorrected. Homogeneity of the compounds were checked by TLC on glass plates coated with silica gel G using solvent system, benzene:ethanol:aq. ammonia (50%) (7:2:1). The IR spectra were taken in KBr pellets on a Shimadzu 8201 PC spectrophotometer. NMR spectra were recorded on a Bruker DRX-300 (300 MHz FT NMR) instrument using $CDCl_3$ as solvent and TMS as internal standard.

The FAB mass spectra were recorded on a JEOL-SX 102/DA-6000 mass spectrometer/Data system using Argon/Xenon (6 kV, 10 mA) as the FAB gas. The accelerating voltage was 10 kV and spectra were recorded at room temperature. *m*-Nitrobenzoyl alcohol (NBA) was used as the matrix. Micro estimations for carbon, hydrogen and nitrogen were carried out in elemental analyzer Carlo Erba 1108. The spectral and elemental analysis were carried out at the Sophisticated Analytical Instrumentation Facility, Central Drug Research Institute, Lucknow.

Synthesis of 5-substituted-2-aminobenzenethiols 3a-f.

Six 5-substituted-2-aminobenzenethiols **3a-f**, were prepared by literature reported methods[15-23].

Synthesis of 2-(4-methoxyphenyl)-3-(substituted benzylidene)-flavanone 8a and 8b.

Equimolar quantities of 4-methoxyflavanone and 4-methoxybenzaldehyde, **7a** or 3,4-dimethoxybenzaldehyde, **7b** were dissolved in ice-cold ethanol saturated with dry HCl gas. To this reaction mixture dry hydrogen chloride gas was passed with stirring till the colour changed from light yellow to purple red and the mixture was kept in refrigerator for 24 hr to separate solids. The crude thus obtained was crystallized from dry ethanol to afford the arylidene flavanones, 2-(4-methoxyphenyl)-3-(4-methoxybenzylidene)-flavanone (**8a**, yellow crystals, m.p. 137°C, yield 70%) and 2-(4-methoxyphenyl)-3-(3,4-dimethoxybenzylidene)-flavanone (**8b**, red coloured solid, m.p. 88°C, yield 67%).

General procedure for the preparation of 10-substituted-6-(4-methoxyphenyl)-6*a*,7-dihydro-7-(4-methoxyphenyl/3,4-dimethoxyphenyl)-6*H*[1]benzopyrano[3,4-*c*][1,5] benzothiazepines 10a-l.

5-Substituted-2-aminobenzenethiols **4a-f** and substituted benzylidene flavanones **8a** or **8b** were dissolved in dry ethanol and mixed with catalytic amount of trifluoroacetic acid. The reaction mixture was refluxed for 3 to 4 hr till the colour changed. The crude solid obtained on the removal of solvent, on crystallization from methanol gave the title compounds.

The analytical and spectral data of **10a-l** are given in the **Tables I** and **II**.

Antimicrobial activity

Antibacterial activity. Nutrient agar used as culture media was prepared by taking a mixture of agar-agar (15 g/L), NaCl (5 g/L), beef extract (1.5 g/L), yeast extract (1.5 g/L) and peptic digest of animal tissues (5 g/L) dissolved in one litre of distilled water. The *p*H of the culture media was maintained at 7.4±0.2. The petri plates containing the culture were inoculated with the bacterial suspension and incubated for 30 minutes. The density of bacterial suspension (approximately 10^8 bacteria/mL) is standardized by dilution with sterile saline or broth to a density visually equivalent to Mc Farland standard or barium sulphate standard. Filter paper discs of test and reference compounds of dose 100 μg/disc were placed on these plates and incubated for 40 hr at 37°C. The zone of inhibition was measured and compared with standard compounds. The results have been shown as activity index (**Table III**).

Antifungal activity. The Sabaroud dextrose agar media, used as the culture media was prepared by mixing mycological peptone (10 g/L), dextrose (40 g/L) and agar-agar (15 g/L) in one litre of distilled water. The *p*H of the culture media was maintained at 5.6±0.2. The petri plates containing the culture were inoculated by even streaking of fungal suspension. The density of fungal suspension (approximately 10^8 fungus/mL) is standardized by dilution with sterile saline or broth

Table III—Antimicrobial activity of compounds **10a-l**
(Zone of Inhibitions are in mm)

Compd	*Staphylococcus aureus*	*Pseudomonas aerginosa*	*Candida albicans*
10a	16 (0.80)	10 (0.50)	-
10b	-	19 (0.95)	10 (0.71)
10c	15 (0.75)	10 (0.50)	18 (1.28)
10d	15 (0.75)	20 (1.00)	24 (1.71)
10e	18 (0.90)	17 (0.85)	24 (1.71)
10f	18 (0.90)	14 (0.70)	17 (1.21)
10g	15 (0.75)	-	-
10h	-	20 (1.00)	8 (0.57)
10i	15 (0.75)	-	18 (1.28)
10j	15 (0.75)	20 (1.00)	22 (1.57)
10k	16 (0.80)	15 (0.75)	26 (1.85)
10l	16 (0.80)	12 (0.60)	18 (1.28)

Values in parentheses represent activity index
Zone of Inhibition of gatifloxin for *Staphylococcus aureus* is 20 mm.
Zone of Inhibition of natilmicin for *Pseudomonas aeruginosa* is 20 mm.
Zone of Inhibition of fluconazole for *Candida albicans* is 14 mm.

to a density visually equivalent to Mc Farland standard or barium sulphate standard. The filter paper discs of test and reference compounds of dose of 100 µg/disc were placed onto these plates and incubated for 40 hr at 37°C. The zones of inhibitions were recorded and compared with the zone of inhibition exhibited by the reference compound to determine the activity index (**Table III**).

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