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Synthesis of novel 1-(7-chloro-6-fluoro-1-benzothiazole-2yl)-3-aryl pyrazole as potential antimicrobial agents

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ABSTRACT

Present work deals with the preparation of 3-aryl-1-(7-chloro-6-fluoro-1-benzothiazole-2yl) pyrazole derivative were prepared from the schiff's bases of aromatic ketones with dimethyl formamide and phosphorous oxychloride undergo cyclization forming pyrazole derivatives and undergo formylation on to the pyrazole ring. The structure of the synthesized compounds have been established on the bases of spectral (IR, ^{1}HNMR and Mass) Properties and their elemental analyses. Further, these were tested for anti-bacterial activity against S.aureus ATCC 29213, E.coli ATCC 25922, Pseudomonas aeruginosa MTCC 741 and anti-fungal activity against Aspergilus niger ATCC 1015, Candida albicans ATCC 9025 in cup plate method. Evaluation of the compound revealed moderate to good antimicrobial activity.

Key words: Benzothiazole, pyrazole, acetophenones, Vilsmeier Haack reagent, antibacterial and antifungal activity.

INTRODUCTION

The various pyrazoles and their derivatives are important biological and pharmacological activities. In particular they are used as anti-inflammatory, analgesics, antibacterial, antifungal, antiviral, anti-diabetics and anti-tubercular agents. [1-6]

Benzothiazole are bicyclic ring with multiple application, 2-aminobanzthiazole have been studied extensively and found to have diverse chemical reactivity and broad spectrum of activity, like antimicrobial, antitumor, antihelmentics, antileishmarial, anticonvulsant, anti-inflammatory activity. [7-13]

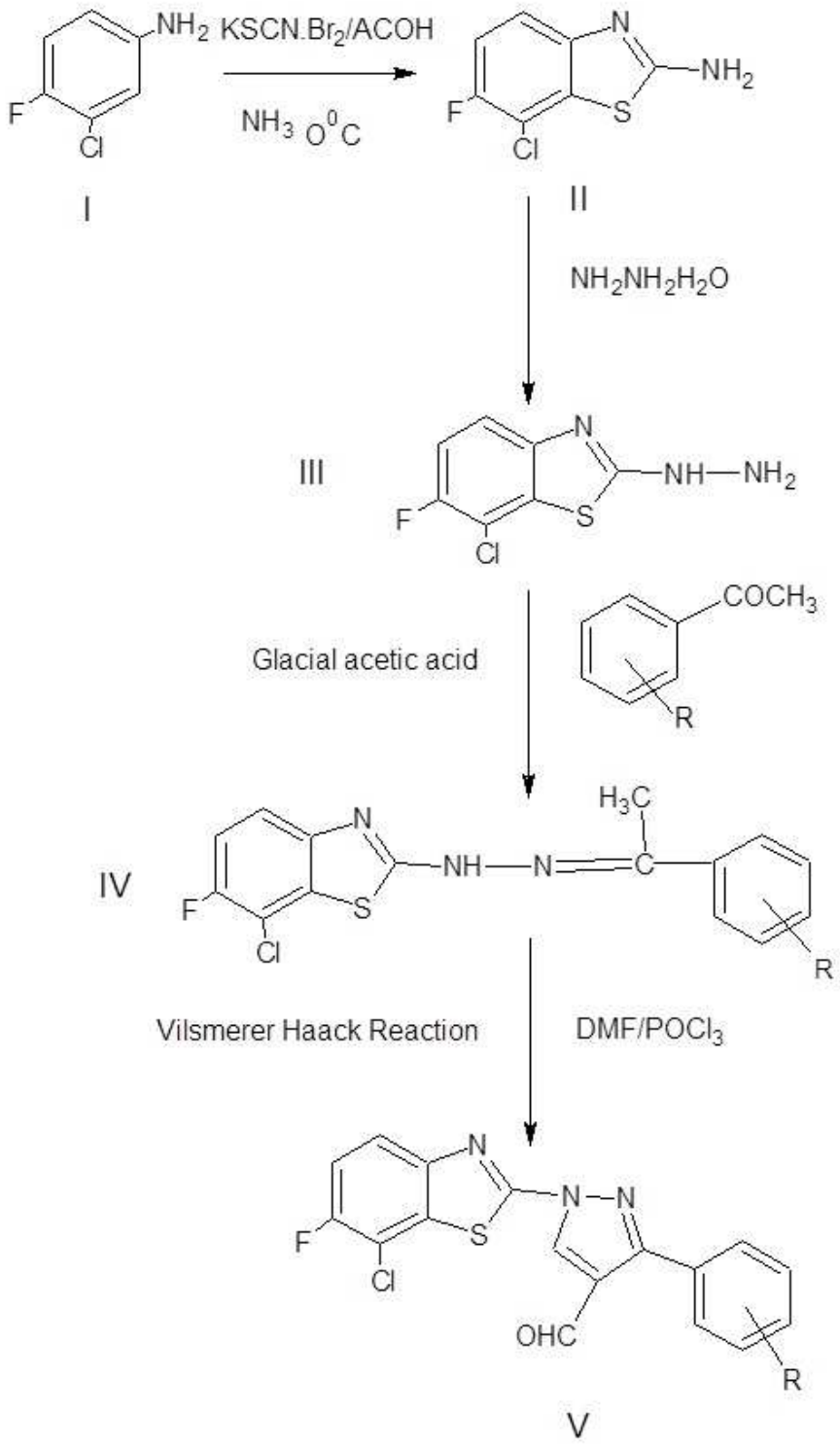
The biological and pharmacological importance of various fluorobenzothiazoles and bearing in the importance of fluorine substitution is imparting enhanced activity. Therefore in continuation, it has been felt worthwhile to synthesis some new chloro-fluorobenzothiazoles in association with pyrazoles with hope of that possess anti-inflammatory, analgesic and antibacterial activities. A synthesis of these compounds involves the starting from 2-amino-7-chloro-6-fluoro benzothiazole, which is converting into corresponding 2-hydrazinobenzothiazole Further, this is exploited to give hydrazones on reacting with different acetophenones and then will Vilsmeier Hack reaction to obtain corresponding formylated benzothiazole. [14-15]

Regarding this, we have synthesized some 1-(7-chloro-6-fluoro-1-benzothiazole-2-yl)-3-aryl pyrazole compounds and derivatives as potential antibacterial and antifungal agents.

MATERIALS AND METHODS

All the chemicals and solvents used, were dried and purified by standard methods, and moisture was excluded from the glass apparatus using CaCl2 drying tubes. The melting points were determined in open capillaries with electronic melting point apparatus. Melting points were determined in open capillary tube and are uncorrected. FT-IR (KBr)

spectra were recorded on SHIMADZU FTIR-8400S Spectrophotometer. ^{1}HNMR spectra of synthesized compounds were recorded on Bruker Spectrophotometer at 300 MHz frequency in Deuterated chloride ($CDCl_3$) as well as dimethyl sulfoxide (DMSO) using tetramethylsilane (TMS) as internal standard (chemical shift δ in ppm). All the compounds were prepared by conventional method as outlined in the scheme I.



R= C_6H_5, 3-OCH_3-C_6H_4, 2NH_2-C_6H_4, 4-Br-C_6H_4, 4-Cl-C_6H_4, 2-Cl-C_6H_4

Synthesis of 7-chloro-6-fluoro-2-aminobenzothiazole (II).
To glacial acetic acid (20ml) cooled below room temperature were added 8gm (0.08mol) of Potassium thiocynate and 1.45gm (0.01mol) of 4-fluoro-3-chloro aniline. The mixture was placed in freezing mixture of ice and salt and mechanically stirred while 1.6 ml of bromine in 6 ml of glacial acetic acid was added, from a dropping funnel at such a rate that the temperature never rise beyond room temperature. The mixture was stirred for 2 hours below room temperature and at room temperature for 10 hours, allowed to stand over night, during which period an orange precipitate settle at the bottom, water (6ml) was added quickly and slurry was heated at 85^0c on a steam bath and filtered hot orange residue was placed in a reaction flask and treated with 10 ml of glacial acetic acid heated again to 85^0c and filtered hot. The combined filtrate was cooled and neutralized with concentrated ammonia solution to P^H 6 a dark yellow precipitate was collected. Recrystallized from benzene, ethanol of (1:1) after treatment with animal charcoal gave yellow plates of 6-fluoro-7-chloro 2-amino (1,3) benzothiazole which is dried in an oven at 80^0c.

Compound (II): Yield: 89 %; m.p. 212^0C; Anal. Calcd. for $C_7H_4ClFN_2S$; C, 63.21; H, 2.12; N, 7.22. Found: C, 62.12; H, 2.51; N, 77.32; IR (KBr, cm^{-1}) 1653 (Ar-CH starching), 3196-3616 (-NH stretching of secondary amine), 2678 (C-H starching) 1253 (C-N). ^{1}H NMR (200 MH_Z, DMSO-d_6, δ/ppm) 2.2 (2H, R-NH_2), 7.1 to 8. 3H, (Ar-H) 10.5 (1H, -CHO); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 36.3 (-NCH_3), 39.9 (-NCH_3), 145.5-156.8 (Ar-C); Mass (m/z): 203 (M^+).

Synthesis of 7-chloro-6-fluoro-2-hydrazinyl-(1,3)benzothiazole (III).
An equimolar amount of concentrated hydrochloric acid (10ml) was added dropwise, with stirring to hydrazine hydrate (0.2mol) at 5-10^0c followed by ethylene glycol (40ml) to the above solution 6-fluoro-7-chloro-2-aminobenzothiazole (0.01mol) was added in portions and resultant mixture was refluxed for 7 hrs, and cooled the solid separates was crystallized from aqueous ethanol.

Compound (III): Yield: 85 %; m.p. -228^0C; Anal. Calcd. for $C_7H_5ClFN_3S$; C, 61.51; H, 1.23; N, 7.19. Found: C, 62.82; H, 2.37; N,87.45; IR(KBr, cm^{-1}) 1663 (Ar-CH), 3296-3416 (-NH stretching of secondary amine.), 2925 (C-H starching) 1262 (C-N). ^{1}H NMR (200 MH_Z, DMSO-d_6, δ/ppm) 2.4 (2H, R-NH_2), 7.1 to 8. 3H, (Ar-H) 10.5 (1H, -CHO); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 34.3 (-NCH_3), 32.9 (-NCH_3), 126.5-139.8 (Ar-C); Mass (m/z): 218 (M^+).

Synthesis of 2(-7-chloro-6-fluoro-1,3-benzothiazole-2-yl)substituted acetophenones hydrazones (VI).
An equimolar amount of compound 7-chloro-6-fluoro-2 hydrazinyl (1,3) benzothiazole (1.5mol), appropriate acetophenone (2.2mol), glacial acetic acid (2-3drop) well taken in absolute ethanol (20ml) and refluxed for 13hrs. On cooling gives corresponding hydrazone of colored crystalline compounds are purified by recrystallization from ethanol and dried under oven.

Compound (VI): Yield: 80 %; m.p. -235^0C; Anal. Calcd. for $C_{15}H_{12}ClFN_3S$; C, 60.61; H, 2.18; N, 7.23. Found: C, 60.12; H, 2.50; N, 75.15; IR (KBr, cm^{-1}) 3255 (-NH_2), 3116 (-NH stretching of secondary amine), 2864 (Ar-H), 1615 (C=N), ^{1}H NMR (200 MH_Z, DMSO-d_6, δ/ppm), 7.513- 7.861(6H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 34.3 (-NCH_3), 34.9 (-NCH_3), 116.5-137.8 (Ar-C); Mass (m/z): 321 (M^+).

Synthesis of Formylated Pyrazolyl Benzothiazole Conventional Method (Va-f)
An equimolar amount mixture of 2(-7-chloro-6-fluoro-1,3-benzothiazole-2-yl)substituted acetophenones hydrazones (1.016 gm, 0.004 mole) was dissolved in 6 mL of DMF and this kept in ice cold condition. To this above mixture Vilsmeier Haack reagent (1.5 mL) of POCl3 was added drop by drop with stirring in (6 mL) and DMF is added with stirring at room temperature for 4 hrs, then content was poured into crushed ice (previously neutralized with $NaHCO_3$ or liq.NH_3) solid separates out which was filter washed with water, dried and recrystallized from ethanol.
Compound (Va): Yield: 85 %; m.p. -260^0C; Anal. Calcd. for $C_{17}H_9ClFN_3OS$; C, 61.68; H, 2.16; N, 8.31. Found: C, 62.82; H, 2.37; N,87.45; IR (KBr, cm^{-1}) 3250 (-NH_2), 3043 (-NH stretching of secondary amine), 2979 (Ar-H), 1615 (C=N), ^{1}H NMR (200 MH_Z, DMSO-d_6, δ/ppm) 7.266(s,1H,of pyrazole), 7.896(s,1H,-CHO), 7.513- 7.861(m,6H,Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 28.4 [-N(CH_2CH_3)$_2$], 29.2 (CH_3), 34.3 (-NCH_3), 34.9 (-NCH_3), 116.5-137.8 (Ar-C), 126.2 [-N(CH_2CH_3)$_2$], 169.8 (-N-CH_2-N-), 189.8 (C=O), 193.2 (C=O); Mass (m/z): 356 (M^+).

Compound (Vb): Yield: 88 %; m.p. -270^0C; Anal. Calcd. for $C_{20}H_{13}ClFN_3O_3S$; C, 62.18; H, 1.16; N, 5.31. Found: C, 62.20; H, 1.37; N, 5.45; IR (KBr, cm^{-1}) 3252 (-NH_2), 3055 (-NH stretching of secondary amine), 29888 (Ar-H), 1615 (C=N), ^{1}H NMR (200 MH_Z, DMSO-d_6, δ/ppm) 7.266(s,1H,of pyrazole), 7.89(s,1H,-CHO), 7.513-7.821(m,6H,Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 29.4 [-N(CH_2CH_3)$_2$], 27.2 (CH_3), 39.3 (-NCH_3), 35.9 (-NCH_3), 116.5-137.8 (Ar-C), 126.2 [-N(CH_2CH_3)$_2$], 168.8 (-N-CH_2-N-), 189.8 (C=O), 193.2 (C=O); Mass (m/z): 343 (M^+).

Compound (Vc): Yield: 82 %; m.p. -280^0C; Anal. Calcd. for $C_{19}H_{12}ClFN_4O_2S$; C, 62.68; H, 2.36; N, 8.31. Found: C, 62.92; H, 2.37; N,87.55; IR (KBr, cm^{-1}) 3234 (-NH_2), 3243 (-NH stretching), 2979 (Ar-H), 1615 (C=N), ^{1}H NMR

(200 MH_Z, DMSO-d_6, δ/ppm) 7.266(s,1H,of pyrazole), 7.896(s,1H,-CHO), 7.573- 7.861(m,6H,Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 28.4 [-$N(CH_2CH_3)_2$], 54.8 (CH_3), 76.8 (-NCH_3), 66.8 (-NCH_3), 133.8-137.8 (Ar-C), 129.2 [-$N(CH_2CH_3)_2$], 170.8 (-N-CH_2-N-), 199.8 (C=O), 193.2 (C=O); Mass (m/z): 351 (M^+).

Compound (Vd): Yield: 73 %; m.p. -211^{0}C; Anal. Calcd. for $C_{19}H_{10}$ $ClFN_3O_2S$ Br; C, 60.68; H, 2.36; N, 8.91. Found: C, 65.82; H, 2.97; N,89.45; IR (KBr, cm^{-1}) 3280 (-NH_2), 3943 (-NH), 2979 (Ar-H), 1615 (C=N), ^1H NMR (200 MH_Z, DMSO-d_6, δ/ppm) 7.266(s,1H,of pyrazole), 7.896(s,1H,-CHO), 7.513- 7.861(m,6H,Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 27.4 [-$N(CH_2CH_3)_2$], 28.2 (CH_3), 38.3 (-NCH_3), 38.9 (-NCH_3), 166.5-127.8 (Ar-C), 128.2 [-$N(CH_2CH_3)_2$], 179.8 (-N-CH_2-N-), 199.8 (C=O), 199.2 (C=O); Mass (m/z): 322 (M^+).

Compound (Ve): Yield: 80 %; m.p. -290^{0}C; Anal. Calcd. for $C_{19}H_{10}Cl_2FN_3O_2S$; C, 68.68; H, 2.16; N, 8.31. Found: C, 62.82; H, 2.87; N,87.45; IR (KBr, cm^{-1}) 3250 (-NH_2), 3043 (-NH), 2379 (Ar-H), 1615 (C=N), ^1H NMR (200 MH_Z, DMSO-d_6, δ/ppm) 7.966(s,1H,of pyrazole), 7.796(s,1H,-CHO), 7.513- 7.861(m,6H,Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 28.4 [-$N(CH_2CH_3)_2$], 27.2 (CH_3), 38.3 (-NCH_3), 34.9 (-NCH_3), 116.5-137.8 (Ar-C), 126.2 [-$N(CH_2CH_3)_2$], 169.8 (-N-CH_2-N-), 199.8 (C=O), 173.2 (C=O); Mass (m/z): 388 (M^+).

Compound (Vf): Yield: 85 %; m.p. -260^{0}C; Anal. Calcd. for $C_{19}H_{10}Cl_2FN_3O_2S$; C, 64.68; H, 2.76; N, 8.55. Found: C, 62.55; H, 2.88; N,87.66; IR (KBr, cm^{-1}) 3650 (-NH_2), 3143 (-NH), 2989 (Ar-H), 1644 (C=N), ^1H NMR (200 MH_Z, DMSO-d_6, δ/ppm) 7.276(s,1H,of pyrazole), 7.896(s,1H,-CHO), 7.813- 7.871(m,6H,Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 27.4 [-$N(CH_2CH_3)_2$], 28.2 (CH_3), 33.3 (-NCH_3), 33.9 (-NCH_3), 166.5-157.8 (Ar-C), 146.2 [-$N(CH_2CH_3)_2$], 165.8 (-N-CH_2-N-), 155.8 (C=O), 143.2 (C=O); Mass (m/z): 390 (M^+).

Antibacterial activity

The antibacterial activity of synthesized compounds was evaluated by the agar well diffusion method. All the bacterial cultures were adjusted to 0.5 McFarland standards, which is visually comparable to a bacterial suspension of approximately 1.5 ×10^8 *cfu/ml*. 10 *mL* of nutrient agar medium was poured into each Petri plate and plates were swabbed with 100 *µL* inocula of the test microorganisms and kept for 10 to 15 *min* for adsorption. Using sterile cork borer of 8 to 10*mm* diameter, wells were bored into the seeded agar plates and these were loaded with a 100 *µL* volume with concentration of 2.0 *mg* mL^{-1} of each cpupounds reconstituted in the dimethylsulphoxide (DMSO). All the plates were incubated at 37ºC for 24 hrs. Antibacterial activity of each organotin complex was evaluated by measuring the zone of growth inhibition against the test organisms with zone reader (HiAntibiotic zone scale). DMSO was used as a negative control whereas Ciprofloxacin was used as positive control. [16] This procedure was performed in three replicate plates for each organism.

Determination of minimal inhibitory concentration

The synthesized compounds were dissolved in DMF to prepare a stock solution of 1 *mg/ml* conc. with this stock solution different dilutions 800 *µg* to 5 *µg/ml* were prepared. The ciprofloxacin was also prepared in DMF to obtain a conc. of 800 *µg/ml* to 5 µg/ml. The sterile test tube containing 1 ml of sterile media were added with 1 ml of different serially diluted test samples. To these tubes 0.1 ml of normal saline solution suspended with respective microorganisms were inoculated and incubated at 37 ± 2^{0}C for 18 to 24 hrs. [13] The growth in the tubes were observed visually for turbidity and inhibition was determined by lowest concentrations of sample that prevented the development of turbidity. The procedure was repeated to confirm the MIC. [17]

Antifungal activity

The antifungal activity of synthesized compound was evaluated by poisoned food technique. [16-18] The molds were grown on potato-dextrose-agar medium at 25ºC for 7 days and used as inoculate. The 15 *mL* of molten potato-dextrose-agar medium (45ºC) was poisoned by the addition of 100 *µL* volume of each compounds having concentration of 2.0 *mg* mL^{-1} reconstituted in the DMSO, poured into a sterile Petri plate and allowed it to solidify at room temperature. The solidified poisoned agar plates were inoculated at the center with fungal plugs (8mm diameter) obtained from the colony margins and incubated at 25ºC for 7 days. DMSO was used as the negative control whereas Ketoconazole was used as the positive control. The diameter of the zone of inhibition was read with zone reader (HiAntibiotic zone scale). [19-22] Diameter of fungal colonies was measured and expressed as percent mycelial inhibition by applying the formula: Percent inhibition of myelial growth = (dc-dt) / dc × 100; dc = average diameter of fungal colony in negative control sets; dt = average diameter fungal colony in experimental sets. The experiments were performed in triplicate in order to minimize the errors.

RESULTS AND DISCUSSION

The various Schiff's Base derivatives V-a-f were prepared using different aromatic aldehyde and ethanol. The synthesis followed is outlined in scheme I. The derivatives synthesized and subjected it for its antimicrobial

evaluation. The synthesized derivative compounds were assayed in vitro for their antibacterial activity shown in Table I and Minimum inhibitory concentration method are shown in Table II, while the antifungal activity of compound is screened for synthesized derivative compounds which show in Table III.
Table I show zone of inhibition of synthesized compounds.

Table I. Zone of inhibition of synthesized compounds

Sr. No	Compound	Zone of inhibition diameter in (mm)		
		***E.coli* ATCC 25922**	***S.Aureus* ATCC 29213**	***P.aeruginosa* MTCC741**
1	V-a	25	20	17
2	V-b	22	27	24
3	V-c	37	28	40
4	V-d	30	32	29
5	V-e	27	24	25
6	V-f	20	18	17
	Standard	47	46	47
	Control	-	-	-

Note: - 15-20 mm poor activity, 20-25 mm moderate activity, above 25 good activity.
Standard (S) = Ciprofloxacin, Control (C) = DMF

Table. II Anti-bacterial activity data by Minimum inhibitory concentration method

S. No.	Compound code	***S.aureus* ATCC 29213**	***E.coli ATCC* 25922**	***Pseudomonas* aeruginosa MTCC 741**
1	**V-a**	200 µg/ml	50 µg/ml	200 µg/ml
2	**V-b**	50 µg/ml	100 µg/ml	50 µg/ml
3	**V-c**	100 µg/ml	200 µg/ml	100 µg/ml
4	**V-d**	100 µg/ml	200 µg/ml	100 µg/ml
5	**V-e**	200 µg/ml	400 µg/ml	50 µg/ml
6	**V-f**	200 µg/ml	50 µg/ml	200 µg/ml

Antimicrobial evaluation

Antibacterial and Antifungal activity. All the test compounds were evaluated for antibacterial activity against *S.aureus* ATCC 29213, *E.coli* ATCC 25922, *Pseudomonas aeruginosa* MTCC 741 following the agar diffusion method of assay using ciprofloxacin as the reference drug. The results were recorded for each tested complex as the average diameter of inhibition zones of bacterial growth surrounding the well in millimetres.

The compounds **V-b, V-c, V-d, V-e,** exhibited good activity against *S.aureus* ATCC 29213, *P.aeruginosa* MTCC 741 and *E.coli* ATCC 25922 and **V-c, V-d, V-f** exhibited Good activity against *A.niger* ATCC 1015, *C.albicans* ATCC 9025 and other have shown moderate activity against *S.aureus* ATCC 29213, *E.coli* ATCC 25922, *P.aeruginosa* MTCC 741, *A.niger* ATCC 1015, *C.albicans* ATCC 9025.

For minimum inhibitory concentration (MIC) method **V-a, V-b** were found moderately active while, **V-c, V-d, V-e, V-h**, and **V-f** were found to have an average activity compared with standard. Test compounds were found to be more sensitive towards *S.aureus* ATCC 29213 and *Escherichia coli* ATCC 25922 and **V-a, V-e** was found moderately active, while **V-c, V-d** and **V-f** were found to have an average activity compared with standard. Test compounds were found to be more sensitive towards *Aspergillus niger* ATCC 1015 and *Candida albicans* ATCC 9025. Table III. shows antifungal activity of synthesized compound.

Table III. Zone of inhibition synthesized compounds

Sr. No	Compound	Zone of inhibition diameter in (mm)	
		***C.albicans* ATCC 9025**	***A.niger* ATCC 1015**
1	V-a	24	22
2	V-b	20	28
3	V-c	28	38
4	V-d	32	36
5	V-e	24	30
6	V-f	25	32
	Standard	33	44
	Control	-	-

Note: - 0-15 mm poor activity, 15-25 mm moderate activity, above 25 good activity.
Standard(S) = Ketoconazole, Control (C) = DMF

CONCLUSION

Based on various studies such as elemental analysis, IR and 1HNMR spectral studies, the obtained results revealed that the nature of substituent and substitution pattern on the benzene ring may have a considerable impact on the antibacterial and antifungal activities of the synthesized compounds have particular importance, a nitro group has a considerable impact on antibacterial and antifungal activity. The antimicrobial data revealed that the synthesized compound was superior to the other derivatives. The synthesized compound showed remarkable antimicrobial activity.

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