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Synthesis and Antimicrobial Evaluation of Some Condensed New pyrimido [1,2-a] benzimidazole

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ABSTRACT

An efficient synthesis of a novel compound series of ***2-[3,5-bis(trifluoromethyl)phenyl]-4-(substitutedphenyl)-1,4-dihydropyrimido[1,2-a]benzimidazole*** **(*Biginelli reaction)*** was accomplished from (E)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(4-chlorophenyl)prop-2-en-1-one and 1H-benzo[d]imidazol-2-amine Microwave 25 minute heating after the product obtained another method Conventional 7 hrs, with 30 % KOH, Ethanol. Here (E)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(4-chlorophenyl)prop-2-en-1-one(Chalcone) is prepared by 1-(3,5-bis(trifluoromethyl)phenyl)ethanone and different aldehyde with Claisen-Schimidt Condensation.All the newly synthesized compounds were characterized by infrared and ^{1}H nuclear magnetic resonance and mass spectroscopic techniques and by elemental analyses. The newly synthesized compounds were evaluated for their antibacterial and antifungal activity.

Keywords : 4-(benzyloxy)-3-methoxybenzaldehyde, N-(substituted phenyl)-3-oxobutanamide and 2H-1,2,4-triazol-3-amine and N,N'-di methyl formamide

I. INTRODUCTION

3, 5-bis (2- [trifluoromethyl) phenyl] – 4 - (substitutedphenyl) - 1, 4 – dihydropyrimido [1,2-a] benzimidazole and their derivative which relates with fused heterocyclic are very efficient chemical compound of pharmaceutical interest[1] large no. of chemical compound of this series were reported to have various activity like anti-viral,[2,3] xanthine oxide inhibitor represented anticancer,[4] anti-inflammatory,[5,6] antimycobacterial[7], antimicrobial[8,9] activity these new triazolopyrimidine compound are expected to consist potent a activity.[10–13] We synthesize here some new condensed triazolopyrimidine with novel antifungal and antimicrobial activity. In synthesis of this novel series bignilli multicomponent reaction is efficient tool.[14]. This method is still topical. Here starting material or classical building block is replaced by another functional group which are complex starting material which is known as synthetic equivalent. Here solvent is dimethylformamide. In this three component reaction occur at very limited time period which is main benefit of these chemical reactions this is multicomponent reaction.

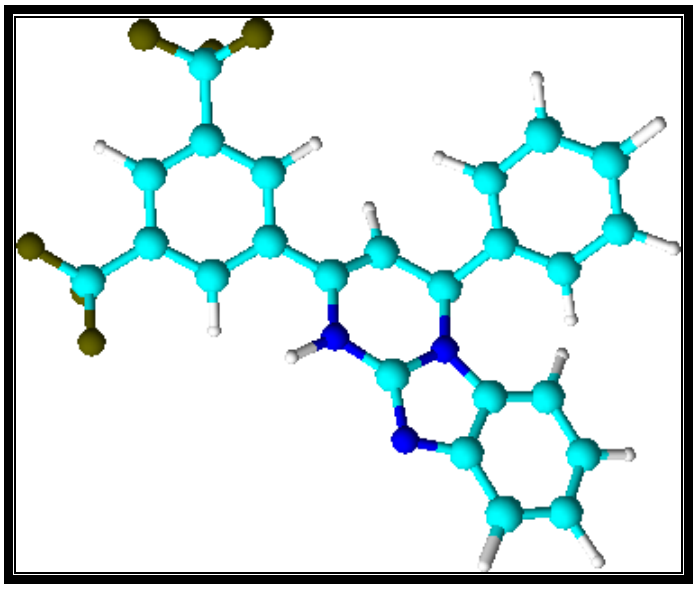
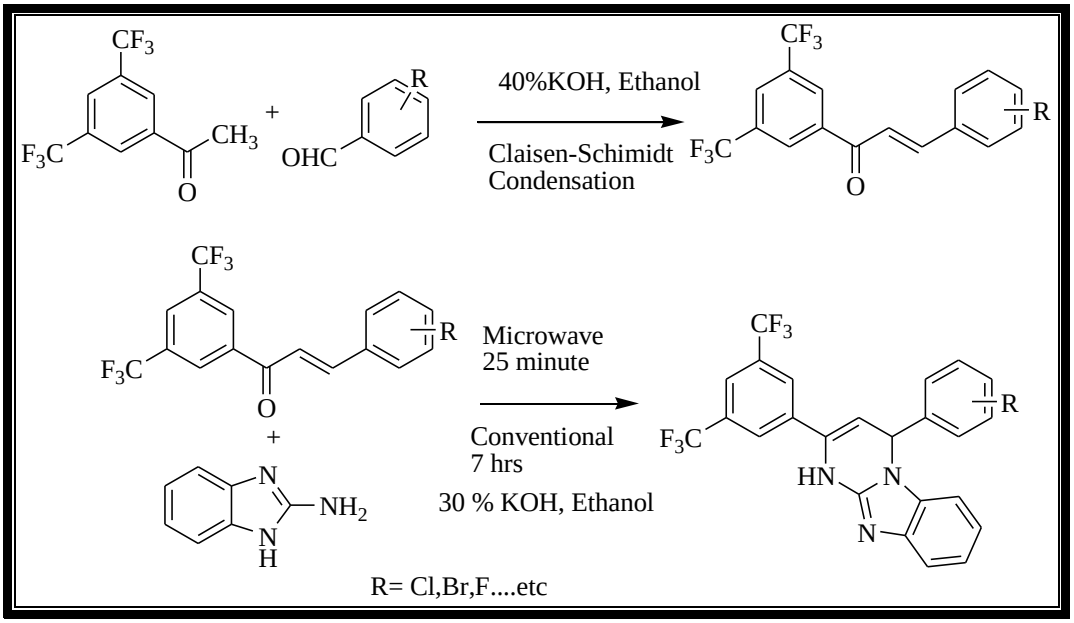


Figure 1. 3D Structure



II. EXPERIMENTAL

Typical untried procedure

A mixture of (E)-1- (3,5-bis (trifluoromethyl) phenyl) - 3- (substituted phenyl) prop-2-en-1-oneand 2-Aminobenzimidazole was (microwave process 25 minute) refluxed in 30% KOH inethanol on the water bath for 7 hours. The solvent was distilled out under vacuum andneutralized with 30% HCl, filter out the solid product and crystalline from ethanol

2-[3,5-bis(trifluoromethyl)phenyl]-4-(4-chlorophenyl)-1,4-dihydropyrimido[1,2-a]benzimidazole (4a)

M.P. 171ºC; Yield: 77%; IR(KBr)(cm^{-1}): 3244 (N-H), 3074, 2847 (C-H), 1607, 1547 (C=C), 1026 (C-F); 754 (C-Cl); ^{1}H NMR (DMSO-*d6*) δ ppm: δ 5.39 (s, 2H, -CH- of pyrimidine ring), 7.14-7.16 (s, 2H, ArH), 7.49-7.50 (s, 1H, ArH), 7.57-7.59 (s, 1H, -ArH),7.68-7.69 (m, 2H, -ArH), 7.80-7.82 (m, 2H, -ArH), 7.90 (m, 3H, -ArH), 8.64 (s, 1H, -NH- of pyrimidine); MS: *m/z* 493. Anal. found: C, 58.39; H, 2.87; Cl, 7.11; F, 23.09; N, 8.50. $C_{24}H_{14}ClF_6N_3$ requires: C, 58.37; H, 2.86; Cl, 7.18; F, 23.08; N, 8.51%.

2-[3,5-bis(trifluoromethyl)phenyl]-4-(4-fluorophenyl)-1,4-dihydropyrimido[1,2-a]benzimidazole (4b)

M.P. 181ºC; Yield: 71%; IR(KBr)(cm^{-1}): 3304 (N-H), 3068, 2828 (C-H), 1600, 1560 (C=C), 1033 (C-F); ^{1}H NMR (DMSO-*d6*) δ ppm: δ 5.40 (s, 2H, -CH- of pyrimidine ring), 7.38-7.42 (m, 1H, ArH), 7.44-7.47 (s, 3H, ArH), 7.49 (s, 1H, -ArH),7.58-7.60 (m, 2H, -ArH), 7.67 (m, 2H, -ArH), 7.82-85 (m, 2H, -ArH), 7.90 (s, 1H, -NH- of pyrimidine; MS: *m/z* 477. Anal. found: C, 60.31; H, 2.90; F, 27.80; N, 8.76. $C_{24}H_{14}ClF_7N_3$ requires: C, 60.38; H, 2.96; F, 27.86; N, 8.80%.

2-[3,5-bis(trifluoromethyl)phenyl]-4-(4-bromophenyl)-1,4-dihydropyrimido[1,2-a]benzimidazole (4c)

M.P. 170ºC; Yield: 75%; IR(KBr)(cm^{-1}): 3249 (N-H), 3063, 2878 (C-H), 1611, 1540 (C=C), 1042 (C-F), 742 (C-Br); ^{1}H NMR (DMSO-*d6*) δ ppm: δ 5.31 (s, 2H, -CH- of pyrimidine ring), 7.35-7.38 (m, 1H, ArH), 7.40-7.43 (s, 3H, ArH), 7.47 (s, 1H, -ArH),7.55-7.58 (m, 2H, -ArH), 7.66 (m, 2H, -ArH), 7.8+-88 (m, 2H, -ArH), 7.97 (s, 1H, -NH- of pyrimidine; MS: *m/z* 538. Anal. found: C, 53.64; H, 2.56; Br, 14.78; F, 21.20; N, 7.77. $C_{24}H_{14}BrF_6N_3$ requires: C, 53.55; H, 2.62; Br, 14.84; F, 21.18; N, 7.81%.

2-[3,5-bis(trifluoromethyl)phenyl]-4-(3-chlorophenyl)-1,4-dihydropyrimido[1,2-a]benzimidazole (4d)

M.P. 179ºC; Yield: 69%; IR(KBr)(cm^{-1}): 3212 (N-H), 3053, 2846 (C-H), 1533, 1502 (C=C), 1032 (C-F), 754 (C-Cl); ^{1}H NMR (DMSO-*d6*) δ ppm: δ 5.30 (s, 2H, -CH- of pyrimidine ring), 7.30-7.32 (m, 1H, ArH), 7.42-7.44 (s, 3H, ArH), 7.53 (s, 1H, -ArH),7.59-7.62 (m, 2H, -ArH), 7.62 (m, 2H, -ArH), 7.80-84 (m, 2H, -ArH), 7.95 (s, 1H, -NH- of pyrimidine); MS: *m/z* 477. Anal. found: C, 60.40; H, 2.98; F, 27.88; N, 8.78. $C_{24}H_{14}ClF_6N_3$ requires: C, 60.38; H, 2.96; F, 27.86; N, 8.80%.

2-[3,5-bis(trifluoromethyl)phenyl]-4-(3-bromophenyl)-1,4-dihydropyrimido[1,2-a]benzimidazole (4e)

M.P. 172ºC; Yield: 77%; IR(KBr)(cm^{-1}): 3265 (N-H), 3057, 2846 (C-H), 1608, 1565 (C=C), 1022 (C-F), 699 (C-Br); ^{1}H NMR (DMSO-*d6*) δ ppm: 5.30 (s, 2H, -CH- of pyrimidine ring), 7.38-7.40 (m, 1H, ArH), 7.45-7.49 (s, 3H, ArH), 7.54 (s, 1H, -ArH),7.59-7.63 (m, 2H, -ArH), 7.65 (m, 2H, -ArH), 7.80-83 (m, 2H, -ArH), 7.99 (s, 1H, -NH- of pyrimidine); MS: *m/z* 538. Anal. found: C, 53.59; H, 2.68; Br, 14.89; F, 21.12; N, 7.75. $C_{24}H_{14}BrF_6N_3$ requires: C, 53.55; H, 2.62; Br, 14.84; F, 21.18; N, 7.81%.

2-[3,5-bis(trifluoromethyl)phenyl]-4-(4-methylphenyl)-1,4-dihydropyrimido[1,2-a]benzimidazole (4f)

M.P. 177ºC; Yield: 78% IR(KBr)(cm^{-1}): 3223 (N-H), 3045, 2856 (C-H), 1589, 1506 (C=C), 1023 (C-F); ^{1}H NMR (DMSO-*d6*) δ ppm: δ 1.13 (s, 1H, CH_3), 5.34 (s, 2H, -CH- of pyrimidine ring), 7.35-7.37 (m, 1H, ArH), 7.40-7.42 (s, 3H, ArH), 7.46 (s, 1H, -ArH),7.54-7.56 (m, 2H, -ArH), 7.62 (m, 2H, -ArH), 7.66-68 (m, 2H, -ArH), 7.88 (s, 1H, -NH- of pyrimidine); MS: *m/z* 473. Anal. found: C, 63.40; H, 3.67; F, 24.11; N, 8.46. $C_{25}H_{17}F_6N_3$ requires: C, 63.43; H, 3.62; F, 24.08; N, 8.88 %.

2-[3,5-bis(trifluoromethyl)phenyl]-4-(4-nitrophenyl)-1,4-dihydropyrimido[1,2-a]benzimidazole (4g)

M.P. 186ºC; Yield: 71%; IR(KBr)(cm^{-1}): 3213 (N-H), 3024, 2853 (C-H), 1611, 1546 (C=C), 1455 (-NO2), 1042 (C-F); ^{1}H NMR (DMSO-*d6*) δ ppm: δ 5.34 (s, 2H, -CH- of pyrimidine ring), 7.30-7.32 (m, 1H, ArH), 7.36-7.38 (s, 3H, ArH), 7.41 (s, 1H, -ArH),7.56-7.58 (m, 2H, -ArH), 7.61 (m, 2H, -ArH), 7.84-86 (m, 2H, -ArH), 7.94 (s, 1H, -NH- of pyrimidine); MS: *m/z* 504. Anal. found: C, 57.54; H, 3.41; F, 22.87; N, 11.46. $C_{24}H_{14}F_6N_4O_2$ requires: C, 57.15; H, 2.80; F, 22.60; N, 11.11%.

2-[3,5-bis(trifluoromethyl)phenyl]-4-(4-methoxyphenyl)-1,4-dihydropyrimido[1,2-a]benzimidazole (4h)

M.P. 174ºC; Yield: 76%; IR(KBr)(cm^{-1}): 3253 (N-H), 3067, 2842 (C-H), 1557,1504 (C=C), 1263 (C-O-C), 1046 (C-F); ^{1}H NMR (DMSO-*d6*) δ ppm: δ 3.45 (s, 3H, -OCH_3), 5.32 (s, 2H, -CH- of pyrimidine ring), 7.32-7.34 (m, 1H, ArH), 7.42-7.44 (s, 3H, ArH), 7.50-7.52 (s, 1H, -ArH),7.56-7.58 (m, 2H, -ArH), 7.78 (m, 2H, -ArH), 7.86-88 (m, 2H, -ArH), 7.98 (s, 1H, -NH- of pyrimidine); MS: *m/z* 489. Anal. found: C, 61.89; H, 3.54; F, 23.35; N, 8.67. $C_{25}H_{17}F_6N_3O$ requires: C, 61.35; H, 3.50; F, 23.29; N, 8.59 %.

2-[3,5-bis(trifluoromethyl)phenyl]-4-(3-methylphenyl)-1,4-dihydropyrimido[1,2-a]benzimidazole (4i)

M.P. 168ºC; Yield: 70% IR(KBr)(cm^{-1}): 3212 (N-H), 3012, 2832 (C-H), 1578, 1501 (C=C), 1045 (C-F); ^{1}H NMR (DMSO-*d6*) δ ppm: δ 1.21 (s, 1H, CH_3), 5.31 (s, 2H, -CH- of pyrimidine ring), 7.36-7.38 (m, 1H, ArH), 7.42-7.44 (s, 3H, ArH), 7.47 (s, 1H, -ArH),7.54-7.56 (m, 2H, -ArH), 7.69 (m, 2H, -ArH), 7.67-7.70 (m, 2H, -ArH), 7.90 (s, 1H, -NH- of pyrimidine); MS: *m/z* 473. Anal. found: C, 63.33; H, 3.63; F, 24.10; N, 8.438. $C_{25}H_{17}F_6N_3$ requires: C, 63.43; H, 3.62; F, 24.08; N, 8.88 %.

2-[3,5-bis(trifluoromethyl)phenyl]-4-(3-methoxyphenyl)-1,4-dihydropyrimido[1,2-a]benzimidazole (4h)

M.P. 167ºC; Yield: 64%; IR(KBr)(cm^{-1}): 3244 (N-H), 3068, 2815 (C-H), 1547,1511 (C=C), 1260 (C-O-C), 1055 (C-F); ^{1}H NMR (DMSO-*d6*) δ ppm: δ 3.40 (s, 3H, -OCH_3), 5.31 (s, 2H, -CH- of pyrimidine ring), 7.30-7.33 (m, 1H, ArH), 7.43-7.45 (s, 3H, ArH), 7.54-7.56 (s, 1H, -ArH),7.58-7.59 (m, 2H, -ArH), 7.84 (m, 2H, -ArH), 7.95-97 (m, 2H, -ArH), 8.79 (s, 1H, -NH- of pyrimidine); MS: *m/z* 489. Anal. found: C, 61.80; H, 3.58; F, 23.37; N, 8.64. $C_{25}H_{17}F_6N_3O$ requires: C, 61.35; H, 3.50; F, 23.29; N, 8.59 %.

III. BIOLOGICAL EVALUATION

Antimicrobial evaluation

All of the synthesized compounds **4a-j** were tested for their antibacterial and antifungal activity (MIC) in vitro by broth dilution method[15-17] with two Gram-positive bacteria Staphylococcus aureus MTCC-96, Streptococcus pyogenes MTCC 443, two Gram-negative bacteria Escherichia coli MTCC 442, Pseudomonas aeruginosa MTCC 441 and three fungal strains Candida albicans MTCC 227, Aspergillus Niger MTCC 282, Aspergillus clavatus MTCC 1323 taking ampicillin, chloramphenicol, norfloxacin, nystatin, and griseofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture Collection (MTCC) and Gene Bank, Institute of Microbial Technology, Chandigarh, India.

The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, specified as the humble concentration of the compound preventing the observable growth, were determined by using the microdilution broth method according to NCCLS(National Committee for Clinical Laboratory Standards) standards.

Serial dilutions of the test compounds and reference drugs were prepared in Mueller-Hinton agar. Drugs (10 mg) were dissolved in dimethylsulfoxide (DMSO, 1 mL). Further progressive dilutions with melted Mueller-Hinton agar were performed to obtain the required concentrations. In primary screening 1000 µg mL-1, 500 µg mL-1 and 250 µg mL-1 concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in the second set of dilution at 125 µg mL-1, 62.5 µg mL-1, 50 µg mL-1, 25 µg mL-1, 12.5 µg mL-1, and 6.250 µg mL-1 concentration against all microorganisms. The tubes were inoculated with 108 CFU mL-1 (colony-forming unit/mL) and incubated at 37 ºC for 24 h. The MIC

was the lowest concentration of the tested compound that yields no visible growth (turbidity) on the plate. To ensure that the solvent did not affect the bacterial growth, a control was performed with the test medium supplemented with DMSO at the same dilutions as used in the experiments and it was observed that DMSO did not affect the microorganisms in the concentrations studied. The results obtained from antimicrobial susceptibility testing are depicted.

Table 1 :- *in vitro Antibacterial Screening Results for* (4a-j)

Code	Minimal inhibition concentration (µg mL^{-1})			
	Gram-positive		Gram-negative	
	GPA1	**GPA2**	**GNA3**	**GNA4**
4a	100	500	250	1000
4b	1000	500	1000	250
4c	1000	250	500	1000
4d	500	500	500	500
4e	250	250	500	500
4f	500	500	100	1000
4g	1000	500	250	250
4h	250	250	250	500
4i	500	500	1000	1000
4j	1000	1000	1000	500
Ampicillin	250	100	100	100
Chloramphenicol	50	50	50	50
Norfloxacin	10	10	10	10
	Staphylococcus aureus	**GPA1**		
	Streptococcus pyogenes	**GPA2**		
	Escherichia coli	**GNA3**		
	Pseudomonas aeruginosa	**GNA4**		

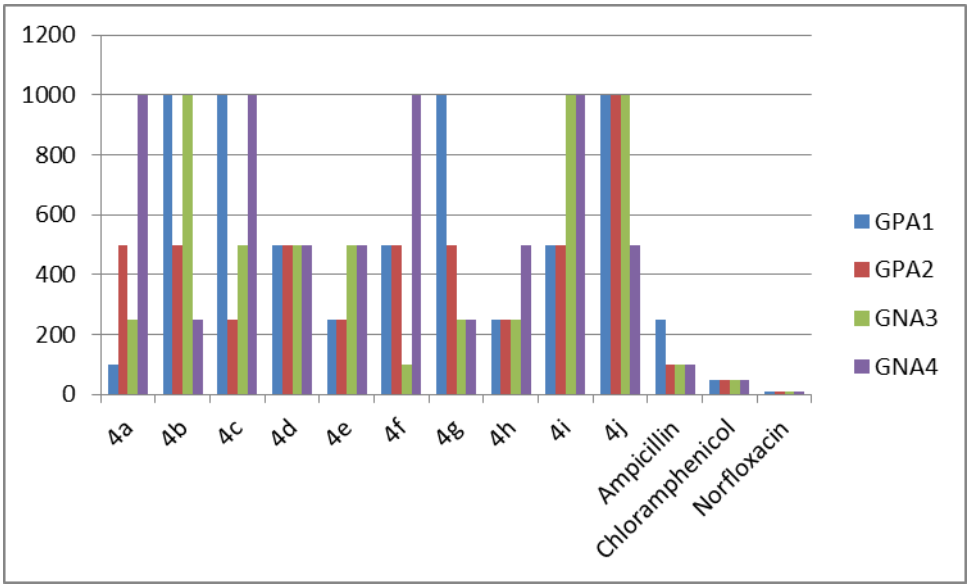
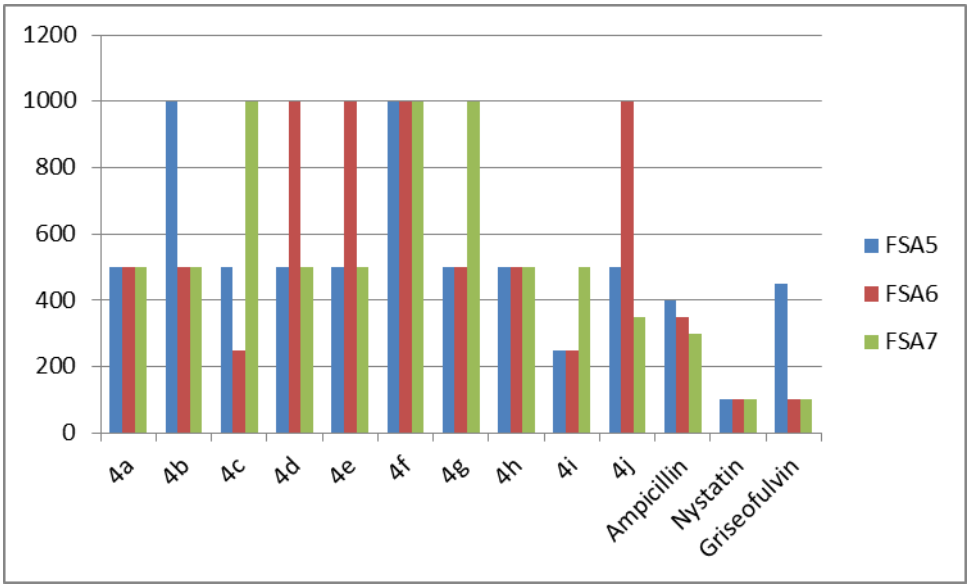


Table 2 :- *in vitro Antifungal Screening Results for* (4a-j)

Code	**Minimal inhibition concentration (µg mL-1)**		
	Fungal species		
	FSA5	**FSA6**	**FSA7**
4a	500	500	500
4b	1000	500	500
4c	500	250	1000
4d	500	1000	500
4e	500	1000	500
4f	1000	1000	1000
4g	500	500	1000
4h	500	500	500
4i	250	250	500
4j	500	1000	350
Ampicillin	400	350	300
Nystatin	100	100	100
Griseofulvin	450	100	100
		Candida albicans	**FSA5**
		Aspergillus Niger	**FSA6**
		Aspergillus clavatus	**FSA7**



IV. RESULT AND DISCUSSION

Here we screened a total of ten compounds for their antimicrobial evaluation. Here 4a compound is an excellent antimicrobial agent with value 100 µg mL-1 and compound 4e and 4h shows good activity with 250 µg mL-1 against Staphylococcus aureus. 4c,4e, 4h compound are good inhibitor against streptococcus pyogenes .4f is excellent inhibitor with a value of 100 micrograms per ml and 4a,4g, 4h is exhibit good activity at 250 µg mL-1 against E.coli .4b,4g exhibit good activity at 250 µg mL-1.

Results of antifungal screening

Here we tested 10 compounds against 3 fungal species. 4i at 250 μg mL-1 shows excellent antifungal activity against at 250 μg mL-1 and other are good inhibitors except for 4b and 4h against candida Albicans 4c and a4i are excellent inhibitor and 4a, 4b, 4g, 4h. good inhibitor at 500 μg mL-1 against aspergillus niger. Except for 4f, 4c, 4g all are moderate inhibitor against aspergillus clavatus.

V. CONCLUSION

We have discussed here a small approach for preparation of 2 - [3,5-bis(trifluoromethyl) phenyl]-4-(substituted phenyl)-1,4-dihydropyrimido [1,2a] benzimidazol and derivative synthesized compounds were screened for antimicrobial activity and antifungal activity from observation we can conclude that by modification of bengilli reaction we can impart the activity of triazolopyrimidine and derivative this work will be useful for understanding the various acts of triazolopyrimidine.

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