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Synthesis, Characterization and Biological evaluation of some Novel Pyrazolo[3,4-b]pyridin-3-amine derivatives

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Abstract: Some *2-aryl(or hetero aryl)-4,6-bis (trifluoromethyl) -2H -pyrazolo [3,4-b]pyridin-3-amine* derivatives have been synthesized by the reaction of substituted aryl or hetero aryl hydrazine with *2-chloro-4,6-bis(trifluoromethyl)nicotinonitrile* [obtained by the reaction of *1,1,1,5,5,5-hexafluoropentane-2,4-dione* with malonamide followed by reaction with phosphorous oxychloroide] in presence of triethyl amine in ethanol . All the synthesized compounds were characterized by elemental analysis, IR, ^{1}H NMR and LCMS. These were screened for in-vitro antimicrobial activity against two gram positive (*Streptococcus Pyogenes* and *Staphylococcus aureus*) and two gram negative bacteria (*Pseudomonas aeruginosa* and *Escherichia coli*) as well as for antifungal and antimalarial activity against plasmodium falciparum strain.

Keywords: Hexafluoropentane-2,4-dione, Malonamide, Phenyl hydrazine, Antimicrobial and Antimalarial activity.

Introduction

A large number of heterocyclic compounds containing pyridine rings are associated with diverse pharmacological properties such as antimicrobial [1, 2], anticancer [3] anticonvulsant [4], antiviral [5], anti-HlV[6], antifungal and antimy-cobacterial activities [7]. Fused pyridines have been attracted considerable attention of researchers due to their great usefulness in synthetic chemistry and due to a very wide spectrum of their biological activities. Pyrazole fused pyridines and pyrimidines are known to possess a wide range of biological activity. Pyrido-[2,3-d]-pyrimidines are heterocyclic ring systems of considerable interest due to several biological activities associated with this scaffold. Some analogues have been found to act as antitumor agents inhibiting dihydrofolate reductases or tyrosine kinases [8, 9], while other are known antiviral agents [10]. The pyrazolo-[3,4-b]-

pyridine framework is a key structural fragment of many heterocyclic compounds showing a broad spectrum of biological activity [11]. Pyrazolo [3,4-b]pyridines are the isosters of bioactive indoles or indazoles [12, 13] and they represent important building blocks in both natural and synthetic bioactive compounds [14]. In the last decade, some heterocycles of this class have been found to regulate the cardiovascular system and possess antiviral [15,16], antileishmanial [17] and antimicrobial properties [18].

Various pyrazolo[3,4-b] pyridines also exhibit pharmacological properties such as anti-inflammatory [19] and anxiolytic activity [20] along with xanthine oxidase inhibitors, cholesterol formation inhibitor and anti-alzheimer [21]. Moreover, pyrazolo[3,4-b] pyridines exhibit promising biological activities including dopamine D3-receptor antagonist, dopamine D4 antagonist [22, 23] and adenosine A1-receptor antagonist [24, 25].

Looking at the importance of these heterocyclic nuclei, it is thought of interest to devote some attention for the synthesis of new substituted pyrazolo[3,4-b]pyridin-3-amine derivatives and to evaluate these derivatives for antimicrobial and antimalarial activity against plasmodium falciparum strain.

2.1 Antimicrobial activity :

All the synthesized compounds were tested against two gram positive bacteria (Staphylococcus aureus, Streptococcus Pyogenes) and two gram negative bacteria (Escherichia coli ,Pseudomonas aeruginosa) using micro broth dilution method [26-29] for the determination of minimal inhibition concentration . For the antifungal activity the common standard strains that were used, are C.Albicans, A,Niger and A.Clavatus. Muller Hinton broth (Microcare laboratory & Tuberculosis Research Centre, Surat-3, India) was used as nutrient medium to grow and dilute the drug suspension for the test bacteria. Inoculum Size for Test Strain was adjusted to 10^8 Cfu [Colony Forming Unit] per milliliter by comparing the turbidity. DMSO was used as diluents / vehicle to get desired concentration of drugs to test upon Standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. In primary screening 1000 µg/ml, 500 µg/ml, and 250 µg/ml concentrations of the synthesized compounds were taken. The active synthesized compounds found in this primary screening were further tested in a second set of dilution against all microorganisms. The highest dilution showing at least 99 % inhibition zone is taken as MIC. The test mixture should contain 10^8 organism/ml. Standard drugs Ampicillin and Chloramphenicol were used as antibacterial for comparison. Standard drugs Nystatin and Greseofulvin were used as antifungal for comparison.

2.2 Antimalarial activity :

The in vitro antimalarial assay was carried out in 96 well microtitre plates according to the microassay protocol reference. The cultures of Plasmodium falciparum strain were maintained in medium RPMI 1640 supplemented with 25 mM HEPES, 1% D-glucose, 0.23% sodium bicarbonate and 10% heat inactivated human serum. The asynchronous parasites of Plasmodium falciparum were synchronized after 5% D-sorbitol treatment to obtain only the ring stage parasitized cells. For carrying out the assay, an initial ring stage parasitaemia of 0.8 to 1.5% at 3% haematocrit in a total volume of 200 µ l of medium RPMI-1640 was determined by Jaswant Singh Bhattacharya (JSB) staining to assess the percent parasitaemia (rings) and uniformally maintained with 50% RBCs (O+). A stock solution of 5mg/ml of each of the test samples was prepared in DMSO and subsequent dilutions were prepared with culture medium. The diluted samples in 20 µ

l volume were added to the test wells so as to obtain final concentrations (at five fold dilutions) ranging between 0.4 μ g/ml to 100 μ g/ml in duplicate well containing parasitized cell preparation. The culture plates were incubated at 37 °C in a candle jar. After 36 to 40 h incubation, thin blood smears from each well were prepared and stained with JSB stain. The slides were microscopically observed to record maturation of ring stage parasites into trophozoites and schizonts in presence of different concentrations of the test agents. The test concentration which inhibited the complete maturation into schizonts was recorded as the minimum inhibitory concentrations (MIC). Quinine was taken as the reference drug.

3.MATERIALS AND METHODS

3.1 General Procedures:

Reagent grade chemicals were used without further purification. All the melting points were taken in open capillaries and are uncorrected. The purity and mass of the synthesized compounds was checked by LCMS . 1H NMR spectral was recorded in CDCl3 /DMSO with tetra methylsilane (TMS) as the internal standard at 400 MHz on a Bruker DRTX-400 spectrophotometer. The chemical shifts are reported as parts per million (ppm). Elemental analysis was performed using a (EURO EA 3000 instrument). Acme silica gel-G and Merck silica gel (100 to 200, 60 to 120 meshes) were used for analytical TLC and Column chromatography respectively.

3.2 Chemistry:

We have prepared the novel pyrazolo [3,4-b]pyridine-3-amine in three steps, using 1,1,1,5,5,5-hexafluoropentane-2,4-dione, malonamide and substituted aryl(or heteroaryl) hydrazine as the starting materials. 1,1,1,5,5,5-hexafluoropentane-2,4-dione on reaction with malonamide in sulfolane results 2-hydroxy-4,6-bis(trifluoromethyl) nicotinamide which on reaction with phosphorous oxychloride and further by cyclisation with substituted aryl hydrazine in presence of triethy amine in ethanol results the desired pyrazolo [3,4-b]pyridine-3-amine derivatives. The clear procedure for the preparation of desired pyrazolopyridine was given below.

4.Preparation of new substituted desired pyrazolo [3,4-b]pyridine-3-amine derivative :

4.1 Procedure for the synthesis of 2-hydroxy-4,6-bis(trifluoromethyl) nicotinamide (Intermediate-1) :

To a solution of malonamide (0.01 mole) in Sulfolane 30ml was added 1,1,1,5,5,5-hexafluoropentane-2,4-dione (0.012 mole) dropwise at 0 °C . Then it was stirred at ambient temperature for 30 min and then it was heated at 70 °C for 4 hrs. The reaction mixture was then cooled and poured into ice-cold water. The resulting precipitate was filtered, washed several times with water, dried and recrystallized from ethanol. (Yield: 64.1%)

Spectral data of intermediate-1:

^{1}H-NMR (400MHz, DMSO-d_6): 13.05 (bs, 1H, -OH), 8.01 (bs, 1H, -NH_2), 7.84 (bs, 1H, -NH_2), 7.62 (s,1H, pyridine-H), MS: 275.1 (M+).

4.2 Procedure for the synthesis of 2-chloro-4,6-bis (trifluoromethyl) nicotinonitrile (Intermediate-2) :

A solution of 2-hydroxy-4,6-bis(trifluoromethyl) nicotinamide (0.01mole) in $POCl_3$ (5 mL) was refluxed for 1hr. After completion, the reaction mixture was evaporated and neutralised with Sat. $NaHCO_3$ solution. The compound was extracted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4, evaporated and purified by column chromatography by using 100-200 silica gel at 2% ethyl acetate in hexane which results to give light yellow viscous oil. (Yield: 37.3%)

Spectral data of intermediate-2:
^{1}H-NMR (400MHz, DMSO-d_6): 8.64(s,1H, pyridine-H), MS: 274.8 (M+).

4.3 General procedure for the synthesis of desired 2-substituted aryl (or heteroaryl)-4,6-bis(trifluoromethyl)-2H-pyrazolo[3,4-b] pyridin-3-amine:
To a solution of 2-chloro-4,6-bis (trifluoromethyl) nicotinonitrile (0.01 mole) in ethanol (15 mL) was added triethyl amine (0.015 mole) followed by substituted aryl(or heteroaryl) hydrazine(0.013 mole) and it was refluxed for 2hrs. After completion, the reaction mixture was evaporated and diluted with water. The compound was extracted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4, evaporated and purified by column chromatography by using 100-200 silica gel at 10% ethyl acetate in hexane which results to give compound 3(a-j) Scheme-1.

Spectral data of desired pyrazolo[3,4-b] pyridin-3-amine:
2-(4-fluorophenyl)-4,6-bis (trifluoromethyl) -2H- pyrazolo[3,4-b]pyridin-3-amine (3a) :
IR(cm^{-1}): 3770.5, 3713.5, 3533.6, 3341.9, 1641.3, 1508.2, 1417.9, 1272.7, 1208.9, 1125.8, 1076.2, 988.7, 844.8, 730.6, 678.6; ^{1}H-NMR (400MHz, DMSO-d_6): 7.75-7.72 (m, 2H, Ar-H), 7.51-7.46 (m, 3H, Ar-H), 6.24(bs, 2H, -NH_2), LCMS: 365.2 (M+). Purity: 96.7 %, Anal. Calcd for $C_{14}H_7F_7N_4$: C- 46.17%; H- 1.94%, F- 36.51%, N- 15.38%, Found : C- 46.15%; H- 1.92%, F- 36.50%, N- 15.31%.

2-(4-chlorophenyl)-4,6-bis(trifluoromethyl)-2H-pyrazolo[3,4-b]pyridin-3-amine (3b) :
IR(cm^{-1}): 3894.9, 3777.7, 3707.3, 3577.9, 3472.1, 3203.1, 1711.9, 1643.3, 1503.0, 1419.9, 1358.4, 1274.3, 1218.4, 1180.5, 1129.1, 1085.6, 995.7, 840.9, 791.4, 711.4; ^{1}H-NMR (400MHz, DMSO-d_6): 7.74-7.70 (m,4H, Ar-H), 7.50 (s,1H, Het-H), 6.30(bs, 2H, -NH_2); LCMS: 381.2 (M+). Purity: 99.30 % ,Anal. Calcd for $C_{14}H_7ClF_6N_4$: C- 44.17%, H-1.85%, Cl- 9.31%,F- 29.94%, N- 14.72%, Found : C- 44.13%, H- 1.84%, Cl- 9.29%, F- 29.92%, N- 14.70%.

2-(4-(trifluoromethoxy)phenyl)-4,6-bis(trifluoromethyl)-2H-pyrazolo[3,4-b] pyridin-3-amine (3c):
IR(cm^{-1}): 3889.6, 3777.2, 3700.6, 3545.5, 3347.6, 2361.4, 1618.0, 1509.7, 1417.5, 1353.0, 1268.5, 1190.6, 1132.4, 1077.3, 990.4, 856.5, 736.4, 682.4 ; ^{1}H-NMR (400MHz, DMSO-d_6): 7.85 (d, J = 8.8 Hz, 2H, Ar-H), 7.65 (d, J = 8.8 Hz, 2H, Ar-H), 7.51(s, 1H, Het-H), 6.36 (bs, 2H, -NH_2); LCMS: 431.0(M+). Purity: 91.07%,Anal. Calcd for $C_{15}H_7F_9N_4O$: C- 41.88%, H- 1.64%, F- 39.74%, N- 13.02%, O- 3.72%, Found :C- 41.86%, H- 1.65%, F- 39.71%, N- 13.01%, O- 3.73%.

2-(4-methoxyphenyl)-4,6-bis(trifluoromethyl)-2H-pyrazolo[3,4-b] pyridin-3-amine (3d) :
IR(cm^{-1}): 3776.3, 3478.8, 3304.9, 3201.0, 2899.7, 1685.7, 1634.9, 1510.4, 1422.3, 1273.7, 1186.3, 1128.0, 1017.5, 870.8, 833.4, 728.2, 683.6 ; ^{1}H-NMR (400MHz, DMSO-d_6): 7.94 (d, J = 9.2 Hz, 2H, Ar-H), 7.88 (s, 1H, Het-H), 7.14 (d, J = 9.2 Hz, 2H, Ar-H), 5.79 (bs, 2H, -NH_2), 3.81(s,3H, Ar-OCH_3), LCMS: 377.1 (M+). Purity: 99.75%, Anal. Calcd for $C_{15}H_{10}F_6N_4O$: C- 47.88%, H- 2.68%, F- 30.30%, N- 14.89%, O- 4.25%, Found C- 47.85%, H- 2.65%, F- 30.27%, N- 14.86%, O- 4.22%.

2-(4-chloro-2-fluorophenyl)-4,6-bis(trifluoromethyl)-2H-pyrazolo[3,4-b] pyridin-3-amine (3e) :
IR(cm^{-1}): 3913.5, 3781.2, 3716.7, 3484.8, 3204.8, 1738.7, 1647.3, 1590.4, 1504.3, 1420.6, 1361.1, 1273.3, 1213.7, 1130.0, 1081.7, 992.7, 863.7, 820.4, 727.4 ;^{1}H-NMR (400MHz, DMSO-d_6): 7.86 (dd, J = 10.1Hz, 2.2Hz, 1H, Ar-H), 7.74 (t, J = 8.2Hz,1H, Ar-H), 7.57(dd, J = 1.4 Hz, 8.6 Hz,1H, Ar-H), 7.47 (s,1H, Het-H), 6.57 (bs, 2H, -NH_2), LCMS :399.2 (M+). Purity: 99.96 %, Anal. Calcd for $C_{14}H_6ClF_7N_4$: C- 42.18%, H- 1.52%, Cl- 8.89%, F- 33.36%,

N- 14.05%, Found : C- 42.15%, H- 1.49%, Cl- 8.88%, F- 33.31%, N- 14.01%.

2-o-tolyl-4,6-bis(trifluoromethyl)-2H-pyrazolo[3,4-b]pyridin-3-amine (3f) :
IR(cm^{-1}): 3776.6, 3708.2, 3647.4, 3581.3, 3334.1, 2341.2, 1742.5, 1615.6, 1500.5, 1415.8, 1358.9, 1271.6, 1205.2, 1131.4, 1074.6, 990.0, 856.7, 770.7, 718.1, 678.4 ;^{1}H-NMR (400MHz, DMSO-d_6): 7.56-7.43 (m,5H), 6.09 (bs, 2H, -NH_2), 2.03 (s, 3H, Ar-CH_3) ,.LCMS :361.1 (M+). Purity: 99.73 % , Anal. Calcd for $C_{15}H_{10}F_6N_4$: C- 50.01%, H- 2.80%, F- 31.64%, N- 15.55%, Found : C-49.99%, H- 2.78%, F- 31.62%, N- 15.53%.

4,6-bis(trifluoromethyl)-2-(5-(trifluoromethyl)pyrazin-2-yl)-2H-pyrazolo[3,4-b]pyridin-3-amine (3g) :
IR(cm^{-1}): 3909.1, 3810.1, 3725.0, 3654.7, 3599.8, 3538.5, 3313.5, 2362.5, 1738.8, 1610.8, 1512.4, 1427.7, 1327.8, 1283.0, 1129.8, 993.0, 923.0, 863.7, 796.2, 717.6, 673.1; ^{1}H-NMR(400MHz, DMSO-d_6): 9.62 (s, 1H, Het-H), 9.21 (s, 1H, Het-H), 7.98 (bs, 2H, -NH_2), 7.48 (s, 1H, Het-H), LCMS :417.1 (M+). Purity: 99.15 % , Anal. Calcd for $C_{13}H_5F_9N_6$: C- 37.51%, H- 1.21%, F- 41.08%, N- 20.19%, Found : C- 37.49%, H- 1.19%, F- 41.06%, N- 20.16%.

4,6-bis(trifluoromethyl)-2-(6-(trifluoromethyl) pyrimidin-4-yl)-2H-pyrazolo[3,4-b]pyridin-3-amine (3h) :
IR(cm^{-1}): 3896.3, 3779.3, 3701.1, 3593.4, 3544.5, 3488.2, 3292.9, 1736.0, 1590.0, 1511.4, 1442.7, 1353.7, 1270.9, 1183.6, 1122.0, 995.2, 864.9, 809.7, 745.2, 689.1;^{1}H-NMR (400MHz, DMSO-d_6): 9.49 (s,1H, Het-H), 8.49 (s,1H, Het-H), 8.25 (bs, 2H, -NH_2), 7.47 (s,1H, Het-H), LCMS :417.2 (M+). Purity: 96.7 % , Anal. Calcd for $C_{13}H_5F_9N_6$: C- 37.51%, H- 1.21%, F- 41.08%, N- 20.19%, Found : C- 37.50%, H- 1.17%, F- 41.05%, N- 20.11%.

2-(1-methyl-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-4,6-bis(trifluoromethyl)-2H-pyrazolo[3,4-b]pyridin-3-amine (3i) :
IR(cm^{-1}): 3870.4, 3781.2, 3650.9, 3474.4, 3254.1, 1622.4, 1508.3, 1433.9, 1329.0, 1281.3, 1229.4, 1107.5, 993.3, 931.2, 860.0, 808.3, 715.4; 1H-NMR (400MHz, DMSO-d_6): 8.17 (s,1H, Ar-H), 7.99 (d, J = 8.8 Hz,1H, Ar-H), 7.75 (d, J = 8.0 Hz,1H, Ar-H), 7.65 (bs, 2H, -NH_2), 7.52 (s,1H, Ar-H), 4.15(s, -CH_3),LCMS :469.1 (M+). Purity: 98.60 %, Anal. Calcd for $C_{17}H_9F_9N_6$: C- 43.60%, H- 1.94%, F- 36.51%, N- 17.95%, Found : C- 43.58%, H- 1.91%, F- 36.48%, N- 17.92%.

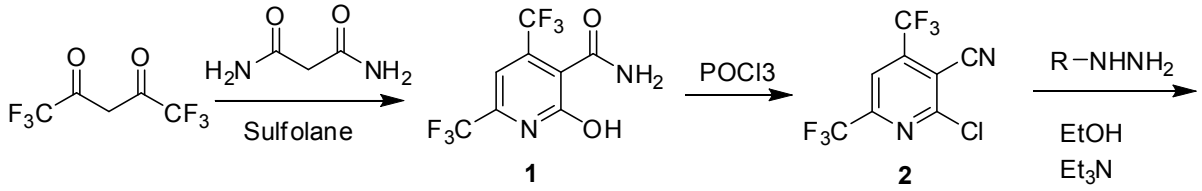
4,6-bis(trifluoromethyl)-2-(2-(trifluoromethyl)imidazo[1,2-b]pyridazin-6-yl)-2H-pyrazolo[3,4-b]pyridin-3-amine (3j) :
IR(cm^{-1}): 3891.4, 3777.1, 3719.0, 3654.0, 3434.9, 3343.2, 3163.6, 2958.4, 2338.3, 1736.8, 1599.6, 1509.5, 1424.7, 1355.0, 1275.3, 1218.5, 1127.4, 998.3, 949.3, 838.3, 790.1, 731.1, 683.7 ;^{1}H-NMR (400MHz, DMSO-d_6): 9.14 (s,1H, Het-H), 8.56 (d, J = 9.6 Hz,1H, Het-H), 8.17 (d, J = 10.0 Hz,1H, Het-H), 7.56 (bs, 2H, -NH_2), 7.50 (s,1H, Het-H), LCMS :456.1 (M+). Purity: 98.64 %, Anal. Calcd for $C_{15}H_6F_9N_7$: C- 39.57%, H- 1.33%, F- 37.56%, N- 21.54%,Found : C- 39.55%, H- 1.31%, F- 37.52%, N- 21.53%.

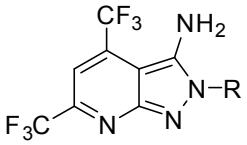
5. Result and discussion

5.1.Chemistry

1,1,1,5,5,5-hexafluoropentane-2,4-dione on reaction with malonamide in sulfolane results 2-hydroxy-4,6-bis(trifluoromethyl) nicotinamide (compound-1) which on reaction with phosphorous oxychloride results 2-chloro-4,6-bis (trifluoromethyl) nicotinonitrile (compound-2). The obtained compound (2) on cyclisation reaction with substituted aryl (or hetero aryl) hydrazine in presence of triethyl amine and ethanol results the desired pyrazolo [3,4-b] pyridine -3-amine derivatives. The list of synthesized compounds are represented by Table-1.

Scheme :





3(a-j)

R = Substituted phenyl, Hetrocycle (Pyrimidine, Pyrazine, Benzimidazole, Imidazo-[1,2-b] pyridazine)

List of Synthesized compound : **Table-1**

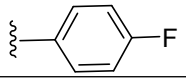
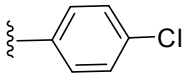
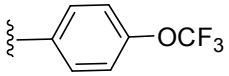
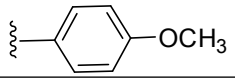
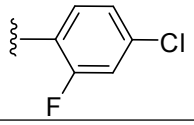
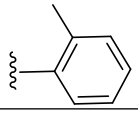
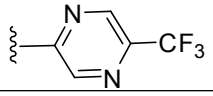
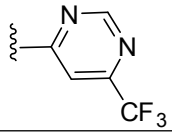
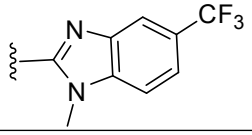
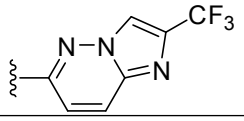
Compound	R	M.P (°C)	Yield (%)
3a		140-142	32.6
3b		176-178	38.2
3c		168-170	41.4
3d		134-135	48.6
3e		194-196	38.1
3f		156-158	35.5
3g		161-163	38.7
3h		147-149	26.3
3i		155-157	25.2
3j		187-189	29.5

Table-2: Antibacterial activity

Compound	S.AUREUS	S.PYOGENUS	E.COLI	P.AERUGINOSA
3a	500	500	250	200
3b	250	250	200	200
3c	500	500	100	125
3d	500	500	62.5	100
3e	100	500	200	500
3f	125	100	250	125
3g	125	125	250	250
3h	125	500	125	500
3i	250	500	250	250
3j	500	250	250	250
Ampicillin	250	100	100	100
Chloramphenicol	50	50	50	50

5.2 Antibacterial activity:

The antibacterial activity of all the synthesized compounds were tested in-vitro against pathogenic E. coli, P.aeruginosa , S.aureus and S.pyogenus and the results were compared with standard drugs (Ampicillin and Chloramphenicol). In case of S.aureus compounds 3e, 3f, 3g and 3h exhibit good activity while compound 3b and 3i show moderate activity and rest of the compounds possess less activity. In case of S.pyogenus compound 3f exhibit good activity while rest of the compound possess less activity. In case of E. coli Compound 3d shows higher activity and compound 3c exhibit good activity while rest of the compounds possess less activity. In case of P.aeruginosa compound 3d and 3f exhibit good activity than the rest of the compounds. The results are given in Table-2.

Table-3: Antifungal activity

Compound	C.Albicans	A.Niger	A.Clavatus
3a	250	>1000	>1000
3b	250	>1000	>1000
3c	500	500	500
3d	500	1000	500
3e	500	500	500
3f	500	1000	500
3g	1000	500	250
3h	500	250	500
3i	500	250	250
3j	250	500	250
Nystatin	100	100	100
Greseofulvin	500	100	100

Table-4 : Antimalarial activity

Compound	Mean IC50 (microgram/ml)
3a	1.05
3b	0.92
3c	0.80
3d	0.58
3e	0.67
3f	0.86
3g	1.10
3h	0.85
3i	0.95
3j	0.97
Quinine	0.268

5.3 Antifungal activity:

The antifungal activity of all the synthesized compounds were tested in-vitro against fungi C.Albicans, A,Niger and A.Clavatus and the results were compared with standard drugs (Nystatin and Greseofulvin). In case of C.Albicans compound 3a, 3b and 3j exhibit good activity while 3c, 3d, 3e, 3f, 3h and 3i show moderate activity and rest of the compounds possess less activity. In case of A,Niger and A.Clavatus all the compounds possess less activity . The results are given in Table-3.

5.4 Antimalarial activity:

For antimalarial activity, Compounds 3d and 3e exhibit good activity closer to reference compound Quinine against plasmodium falciparum strain while rest of the compounds possess less activity. The results are given in Table-4.

6. Conclusion :

All the newly synthesized compounds were screened for antibacterial, antifungal and antimalarial activity. The data in the Table-2 indicate that among the synthesized compounds, compound 3d exhibit excellent and compounds 3c, 3e and 3f possess good antibacterial activity. However, the activities of the tested compounds are much less than those of standard agents used. These compounds also show potent antimalarial activitiy except compound 3c and 3f. From the results of various biological activities it is clear that these compounds would be of better use in drug development to combat bacterial infections and as antimalarial agents in the future.

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