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Study of 5,10-diphenyl-5H-[1,2,4]triazolo[4`,3`:4,5][1,3,4]thiadiazolo[3,2-a] pyrido [3,2-f] quinazolines

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ABSTRACT
Present study consists of design, synthesis of several novel substituted [3,2-f]quinazolines derivatives (3a-e) and antibacterial and antifungal evaluation. The structures of the synthesized derivatives were evaluated by IR, 1H-NMR, Mass and elemental analysis (C, H, N). Compound 3b showed significant antimicrobial spectrum.
Keywords: substituted [3,2-f]quinazolines, antibacterial, antifungal.

INTRODUCTION
Bacterial threatening to society as multi-drug resistance is a big blow and continual drug development program is the only solution. Literature study explored the role of heterocyclic derivatives in the field of medicinal chemistry viz. 1,3,4-thiadiazole [1-4], quinoline [5-6] and triazoles [7-10] were found of great significance due to their versatile biological activities. 3-Phenyl substituted-4-amino-5 –mercapto -1,2,4-triazoles were found of great interest due to their ambient nucleophilic centre and generally employed as starting materials/ molecular manipulation for the synthesis of several interesting potent N-bridged heterocycles. In the current work designing and synthesis was focused on 1,3,4-thiadiazole, quinoline and triazole moieties. By adopting the conventional synthetic strategies several substituted 1,3,4 thiadiazoles were synthesised with the hope that the synthesised derivatives will better biological profile with the minimum amount of toxicity.

RESULTS AND DISCUSSION
Synthesis was started by the reaction of quinolin-5-ol, acetophenone and urea to yield compound **1**, which on further refluxing with phosphorous oxychloride furnished compound **2**. Condensation reaction of compound **2** and 5,10-diphenyl-*5H*-[1,2,4]triazolo[4`,3`:4,5][1, 3,4] thiadiazolo [3,2-a] pyrido [3,2-f]quinazolines **3a-e**. The synthesized compounds **2** and **3a-e** were biologically evaluated for antibacterial and antifungal activity against the selected strains of pathogens (Table-**1** & **2**). The screened derivatives **2** and **3a-e** fungistatic activity at 1.10- 360 µmol/ml while fungicidal activity was achieved at 2.15-745.2 µmol/ml. Among all the tested derivatives, compound **3b** exhibited the highest antifungal potential with MIC at 1.12-2.19 X 10^{-2} µmol/ml and MFC at 2.18.15-4.30 µmol/ml. All the compounds showed brawny antibacterial activity against all bacterial species. MIC for the compounds **2** and **3a-e** were at 0.65-74.5X 10^{-2} µmol/ml and MBC 1.15-125.5X 10^{-2} µmol/ml. This compound showed the best antifungal as well as antibacterial effect among all the tested. Reference drugs were ampicillin (MIC 3.5–25.8 X 10^{-2} µmol/ml and MBC 8.6–51.6 X 10^{-2} µmol/ml) and ketoconazole (MIC 0.60–2.38 X 10^{-2} µmol/ml and MFC 2.38–3.35 X 10^{-2} µmol/ml) for antibacterial and antifungal activity respectively.

EXPERIMENTAL
All the chemicals used for the preparation of desired derivatives, were obtained from Sisco Research Laboratories (SRL), Mumbai, India; Qualigen Fine Chemicals, Mumbai, India; E. Merck Ltd., New Delhi, India. The reference drugs ampicillin and ketoconazole were procured from Ind-Swift, Pharmaceutical, Panjab, India. The melting points of the compounds were determined in open glass capillaries with the help of thermonic melting points apparatus (Campbell Electronics, Mumbai, India) and are uncorrected. The homogeneity of all the newly synthesized compounds was routinely checked by TLC on silica gel G plates and spots were located by using iodine chamber. Elemental analysis was performed in Heraeus CHN rapid analyser. The results were found within the ±0.4% of theoretical values. Infrared spectra were recorded on KBr pellets on a Perkin Elmer system 2000 FTIR spectrometer and 1H- NMR spectra on Bruker DPX 200 using TMS as internal standard.

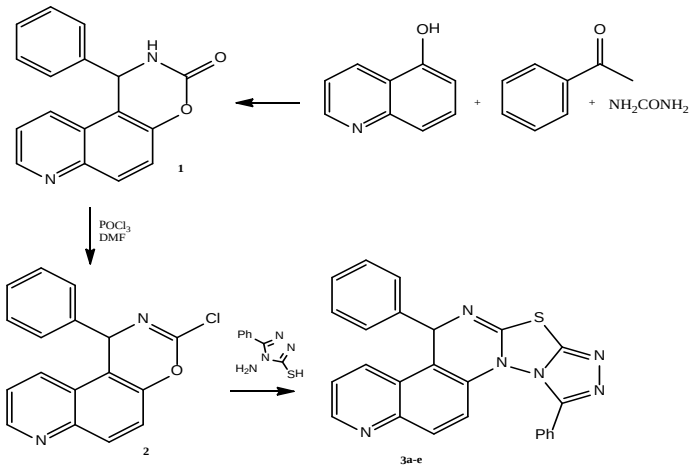
PHARMACOLOGY
All the newly synthesized compounds were screened for their antibacterial and antifungal activity against the clinically isolated and identified microbial strains. The antibacterial assay was carried out by micro dilution method [12-14] while modified micro dilution technique [12-11] was used for the antifungal activity. The minimum inhibitory, bactericidal and fungicidal concentrations (MICs, MBCs and MFCs) were determined by a serial dilution technique using 96-well microtiter plates.

TABLE 1: Antifungal activity of tested compounds (3a-e) (MIC & MFC in µmol/ml × 10-2)

Bacterial strains	Compound 2 MIC MBC	Compound 3a MIC MBC	Compound 3b MIC MBC	Compound 3c MIC MBC	Compound 3d MIC MBC	Compound 3e MIC MBC
B. cereus	74.5 125.2	1.68 2.24	0.65 1.15	2.15 4.10	2.00 2.71	2.00 2.68
S. aureus (ATCC)	37.4 49.5	1.15 2.19	0.80 1.45	1.61 2.15	1.72 2.29	1.30 3.36
E. coli	70.5 122	1.20 1.64	1.08 2.15	2.08 4.20	1.15 2.29	1.70 2.18
P. vulgaris	74.5 125.5	1.10 2.19	1.24 2.60	1.10 2.19	1.79 2.38	1.64 4.38

TABLE 2: Antibacterial activity of the tested compounds (3a-e) (MIC & MBC in µmol/ml × 10-2)

Fungal strains	Compound 2 MIC MFC	Compound 3a MIC MFC	Compound 3b MIC MFC	Compound 3c MIC MFC	Compound 3d MIC MFC	Compound 3e MIC MFC
A. niger	285 660	1.12 2.22	1.10 2.15	1.64 4.38	2.10 6.15	2.14 4.40
A. fumigatus	280 665	2.19 4.38	1.65 4.20	2.20 4.45	1.65 4.32	1.62 4.15
C. albicans	360 740	2.12 4.41	2.19 4.38	2.15 4.35	2.25 6.42	2.26 4.50
C. crusie	360 745.2	4.40 6.57	2.19 4.38	4.42 6.58	4.25 6.24	4.30 6.45



Ph = C_6H_5, 4-Cl.C_6H_4, 2-Cl.C_6H_4, $C_7H_7NO_2$, 4-NO_2.C_6H_4

SCHEME-1

SYNTHESIS

***Preparation of 1-phenyl-1H-[1,3]oxazino[5,6-f]quinolin-3(2H) one* (1)**

A mixture of quinolin-5-ol (0.01 mol), urea (0.01 mol) and acetophenone (0.01 mol) in ethanol was refluxed for 1 hr. The reaction mixture was cooled, poured into ice-water slowly with continuous stirring, filtered and recrystallized by methanol: Yield: 66%; m.p.: 175 ^{0}C; R_f: 0.66. IR (KBr, cm−1): 3410 (NH), 1745 (C=O), 1625 (C…C of aromatic ring), 1590 (C=N), 1290 (C-O-C). ^{1}H-NMR ($CDCl_3$, δ/ppm): 8.60-7.42 (m, 10H, Ar-H), 6.78 (bs, 1H, NH), 4.70 (s, 1H, CH-NH). Anal. calcd. for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14; found C, 73.42; H,4.35; N,10.20. MS (m/z): 276.09.

***Preparation of 3-chloro-1-phenyl-1H-[1,3]oxazino [5,6-f] quinoline* (2)**

Phosphorous oxychloride (0.015 mol) added slowly to a solution of compound 1 (0.01 mol) in toluene. The reaction mixture was refluxed for 2 hrs. Excess of solvent was distilled off. The reaction mixture cooled. The cooled mass poured into ice-water slowly with continuous stirring, neutralized with aqueous 3% KOH solution, filtered and recrystallized by methanol: Yield: 61%; m.p.: 213 0C; R_f: 0.70. IR (KBr, cm−1): 1622 (C…C of aromatic ring), 1594 (C=N), 1288 (C-O-C). ^{1}H-NMR ($CDCl_3$, δ/ppm): 8.52-7.55 (m, 10H, Ar-H), 4.75 (s, 1H, CH-N-C). Anal. calcd. for $C_{17}H_{11}ClN_2O$: C, 69.28; H, 3.76; N, 9.50; found C, 69.31; H,3.80; N,9.63.MS (m/z): 294.06.

***General preparation of 5,10-diphenyl-5H- [1,2,4]triazolo [4`,3`:4,5][1,3,4]thiadiazolo[3,2-a]pyrido [3,2-f]quinazolines* (3a-e)**

The solution of compound 2 (0.002 mol) in isopropanol was refluxed with 2-amino-5-phenyl-1,3,4-thiadiazole (0.002 mol) for 2-3 hours. Excess of solvent was distilled off and the reaction mixture thus obtained was cooled, poured into ice cold water, washed with petroleum ether (40-60°C) and recrystallised with appropriate solvents to furnish the products 3a-e. Compound 3a:

Yield: 68%; m.p.: 240 ^{0}C; R_f: 0.76. IR (KBr, cm−1): 1620 (C…C of aromatic ring), 1591 (C=N), 1369(N-N), 1292 (C-O-C), 670 (C-S-C). ^{1}H-NMR ($CDCl_3$, δ/ppm): 8.55-7.20 (m, 15H, Ar-H), 4.56 (s, 1H, CH-N-C). Anal. calcd. for $C_{25}H_{16}N_6S$: C, 69.43; H,3.73; N, 19.43; found C, 69.38; H,3.67; N,19.58. MS (m/z): 432.12.

CONCLUSION

All the screened derivatives displayed mild to moderate antimicrobial profile but derivative **3b** displayed significant antifungal and antibacterial profiles. Biological data revealed that the diverse substitution was well abided on the substituted [3,2-f]quinazolines for proper fit at the potential receptor site and 4-chlorophenyl substitution enhanced biological activities. It provided broad antifungal as well as antibacterial spectrum to the substituted [3,2-f]quinazolines.

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