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Synthesis, Characterization and Antifungal Activity of Various Substitutedquinazolinone Derivatives Containing Azeti/thiazolidinone Moiety

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Abstract: Quinazolinones 4a -4h, 5a-5h have been synthesised by the cyclodensation of chloroacetyl chloride/ thioglycolic acid with N-N-arylidene derivative (3a-3h) which in turn have been prepared by the action of substituted benzaldehyde on 3-amino-2-methyl-6-bromoquinazoline-4(3H)-one (2). The structures of the synthesized compounds have been confirmed by elemental analysis, IR and ^{1}HNMR spectral data. All the products have been screened for their antifungal activity against several fungi such as A. fumigatus, C. albicans, C. albicans ATCC and C. krusei. The synthesized compounds were compared with standard drug fluconazole.

Key words: Quinazolinones · Azetidinones · Thiazolidinones · Antifungal activity.

INTRODUCTION

Quinazolinon-4-ones have recently attracted attention as an important class of heterocyclic compounds in the field of drugs and pharmaceuticals. These compounds are widely used as antimicrobial activity [1-4], antibacterial activity [5, 6], antifungal activity [7, 8], insecticidal [9] and antiinflammatory [10]. Quinazolinones having azetidinone [11, 12] (commonly known as β-lactam) moeity are found to possess a wide spectrum of antifungal activity. Thiazolidinone [13, 14] moiety with quinazolinones derivatives increases the antifungal activity. In view of the diverse type of biological activity it was thought worthwhile to prepare the title compounds with the hope that quinazolinone derivatives at three positions may prove to be biologically active and evaluate then for antifungal activity.

MATERIALS AND METHODS

All reagents and solvents were of analytical grade and used directly. Reactions were routinely performed in oven-dried borosil glassware. The melting points of compounds were determined in open capillaries with the help of thermonic melting point apparatus and were uncorrected. The homogeneity of all newly synthesized compounds was routinely checked by thin layer chromatography (TLC) on silica gel G plates and spots were located by using iodine chamber. The melting points of compounds were determined in open capillaries and are uncorrected. The homogeneity of the synthesized compounds was routinely checked by thin layer chromatography on silica gel G plates. Elemental analysis (C, H, N) of all the synthesized compounds were determined by perkin-Elmer 2400 elemental analyzer and results were found within the ± 0.4% of theoretical values. The IR spectra were recorded on a Beckman Acculab-10 Spectrometer (í max in cm^{-1}) and the ^{1}HNMR spectra were recorded by Brucker DPX-300MHz using $CDCl_3$ as solvent.

Preparation of 6-Bromo-2-Methyl-4h-Benzo[d] (1, 3) Oxazin-4-one (1): Dissolve the bromoantranilic acids (1.0 mol) in acetic anhydride (100 ml) and acetic acid (50 ml) was added in the mixture with stirring. The reaction mixture was poured on to crushed ice then left overnight at room temperature. The precipitate thus obtained was filtered, dried and recrystallized with appropriate solvents to obtain compound 1. Yield 87% (methanol); m.p. 90°0C. IR (KBr max in cm^{-1}): 610 (C-Br), 1090 (C-O-C), 1570 (C=N), 1610 (C-C of aromatic ring), 1715 (C=O), 3133 (aromatic CH streching); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.07 (s, 3H, CH_3), 7.71-8.50 (m, 3H, Ar-H); Anal. Calcd. For $C_9H_6BrNO_2$: C, 45.03; H, 2.52; N, 5.83; Found: C, 45.05; H, 2.53; N, 5.80%.

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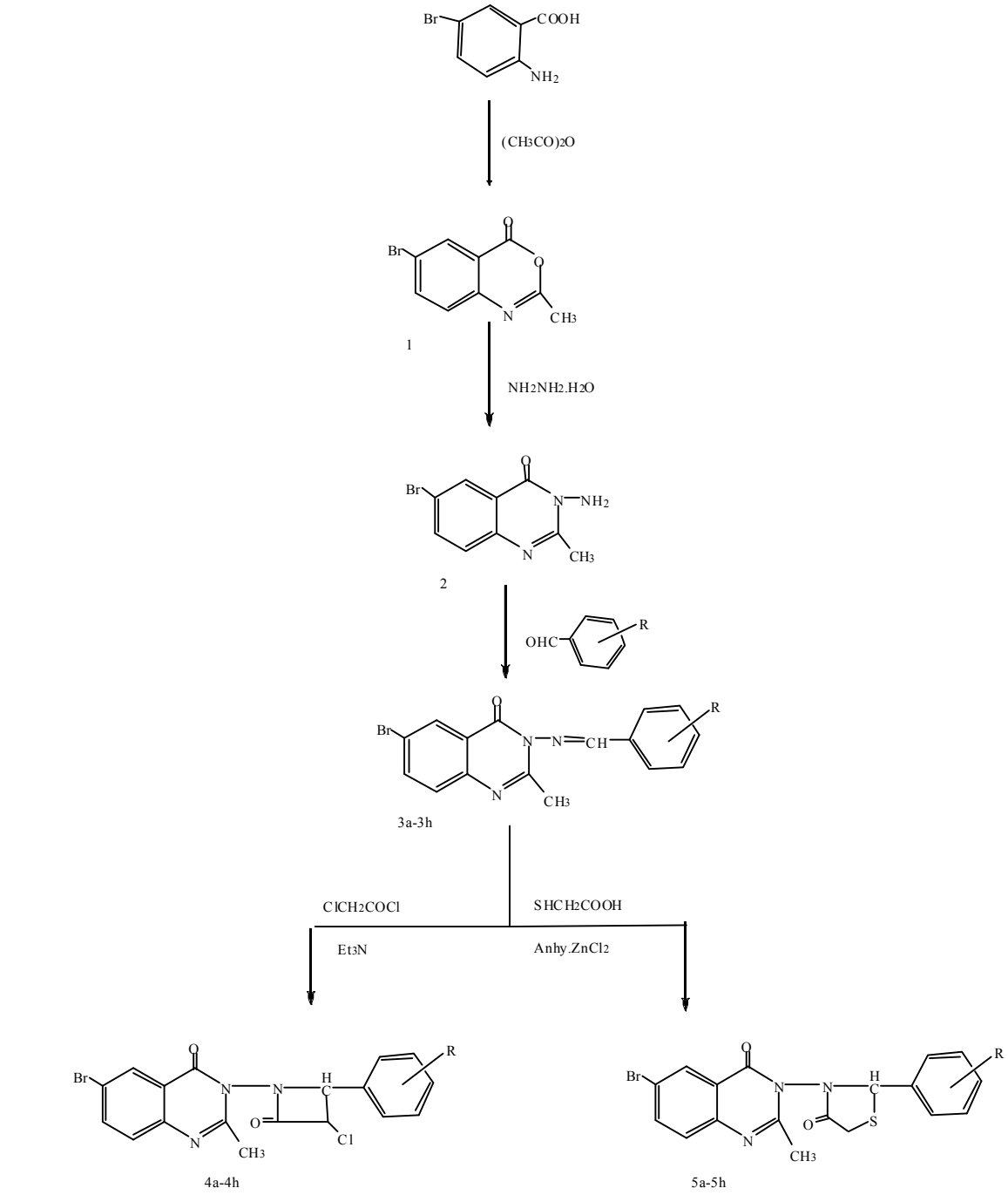


Scheme- 1

Preparation of 3-Amino-6-Bromo-2-Methylquinazolin-4(3h)-One (2): A mixture of compound 1 (1 mol) and hydrazine hydrate (0.4 mol) and ethanol (40 mol) was taken RBF placed in microwave oven and irradiated for 4 min. After completion of reaction (monitored by TLC) mixture was cooled and the resulting solid was filtered, dried and recrystallized from ethanol to yield compound 2. Yield 85% (ethanol); m.p. 99°C. IR (KBr max in cm^{-1}): 612 (C-Br), 1571 (C=N), 1613 (C-C of aromatic ring), 1713 (C=O), 3135 (aromatic CH streching), 3340 (NH_2); ^{1}HNMR

($CDCl_3$ + DMSO-d_6) & in ppm: 2.06 (s, 3H, CH_3), 7.70-8.52 (m, 3H, Ar-H), 9.02 (s, 2H, NH_2 exchangeable with D_2O); Anal. Calcd. For $C_9H_8BrN_3O$: C, 42.54; H, 3.17; N, 16.54; Found: C, 42.51; H, 3.15; N, 16.52%

General Procedure for Preparation of 6-Bromo-3-(Substitutedbenzylideneamino)-2-Methylquinazolin-4(3h)-One (3a-3h): A mixture of compound 2 (0.5 mol) and different substituted benzaldehyde (0.5 mol) in 40 ml of ethanol along with glacial acetic acid (2-3 drops) was refluxed for 12 hr. The reaction mixture was cooled. The solid obtained was filtered, washed with water, dried and recrystallized from appropriate solvents to furnish compounds (3a-3h).

6-Bromo-3-(Benzylideneamino)-2-Methylquinazolin-4(3h)-One (3a): Yield 81% (acetone); m.p. 110°C. IR (KBr max in cm^{-1}): 610 (C-Br), 1284 (N-N), 1508 (C-N), 1572 (C=N), 1610 (C-C of aromatic ring), 1715 (C=O), 3133 (aromatic CH streching); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.05 (s, 3H, CH_3), 7.71-8.51 (m, 8H, Ar-H), 8.83 (s, 1H, N=CH of benzylideneamino); Anal. Calcd. For $C_{16}H_{12}BrN_3O$: C, 56.16; H, 3.53; N, 12.28; Found: C, 56.15; H, 3.50; N, 12.26%

6-Bromo-3-(2-Hydroxybenzylideneamino)-2-Methylquinazolin-4(3h)-One (3b): Yield 78% (methanol); m.p. 100°C. IR (KBr max in cm^{-1}): 613 (C-Br), 1282 (N-N), 1505 (C-N), 1574 (C=N), 1612 (C-C of aromatic ring), 1717 (C=O), 3135 (aromatic CH streching), 3450 (OH); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.07 (s, 3H, CH_3), 7.71-8.52 (m, 7H, Ar-H), 8.85 (s, 1H, N=CH of benzylideneamino), 11.02 (s, 1H, OH exchangeable with D_2O); Anal. Calcd. For $C_{16}H_{12}BrN_3O_2$: C, 53.65; H, 3.38; N, 11.73; Found: C, 53.62; H, 3.34; N, 11.76%

6-Bromo-3-(4-Methoxybenzylideneamino)-2-Methylquinazolin-4(3h)-One (3c): Yield 74% (ethanol); m.p. 116°C. IR (KBr max in cm^{-1}): 613 (C-Br), 1228 (OCH_3), 1287 (N-N), 1503 (C-N), 1574 (C=N), 1613 (C-C of aromatic ring), 1713 (C=O), 3136 (aromatic CH streching); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.06 (s, 3H, CH_3), 3.38 (s, 3H, OCH_3), 7.70-8.52 (m, 7H, Ar-H), 8.88 (s, 1H, N=CH of benzylideneamino); Anal. Calcd. For $C_{17}H_{14}BrN_3O_2$: C, 54.86; H, 3.79; N, 11.29; Found: C, 54.83; H, 3.80; N, 11.26%

6-Bromo-3-(4-Hydroxy-3-Methoxybenzylideneamino)-2-Methylquinazolin-4(3H)-One (3d): Yield 71% (acetone); m.p. 121°C. IR (KBr max in cm^{-1}): 610 (C-Br), 1225 (OCH_3), 1284 (N-N), 1506 (C-N), 1570 (C=N), 1611 (C-C of aromatic ring), 1715 (C=O), 3133 (aromatic CH streching), 3452 (OH); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.09 (s, 3H, CH_3), 3.39 (s, 3H, OCH_3), 7.71-8.50 (m, 6H, Ar-H), 8.87 (s, 1H, N=CH of benzylideneamino), 11.02 (s, 1H, OH exchangeable with D_2O);; Anal. Calcd. For $C_{17}H_{14}BrN_3O_3$: C, 52.60; H, 3.63; N, 10.82; Found: C, 52.63; H, 3.60; N, 10.83%

6-Bromo-3-(2-Chlorobenzylideneamino)-2-Methylquinazolin-4(3H)-One (3e): Yield 70% (methanol); m.p. 130°C. IR (Kbr max in cm^{-1}): 612 (C-Br), 1281 (N-N), 1508 (C-N), 1573 (C=N), 1610 (C-C of aromatic ring), 1718 (C=O), 3131 (aromatic CH streching); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.05 (s, 3H, CH_3), 7.70-8.52 (m, 7H, Ar-H), 8.82 (s, 1H, N=CH of benzylideneamino); Anal. Calcd. For $C_{16}H_{11}BrClN_3O$: C, 51.02; H, 2.94; N, 11.16; Found: C, 51.05; H, 2.50; N, 11.13%

6-Bromo-3-(4-Chlorobenzylideneamino)-2-Methylquinazolin-4(3H)-One (3f): Yield 68% (ethanol); m.p. 128°C. IR (KBr max in cm^{-1}): 615 (C-Br), 1282 (N-N), 1503 (C-N), 1570 (C=N), 1613 (C-C of aromatic ring), 1714 (C=O), 3135 (aromatic CH streching); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.07 (s, 3H, CH_3), 7.71-8.52 (m, 7H, Ar-H), 8.85 (s, 1H, N=CH of benzylideneamino); Anal. Calcd. For $C_{16}H_{11}BrClN_3O$: C, 51.02; H, 2.94; N, 11.16; Found: C, 51.04; H, 2.51; N, 11.12%

6-Bromo-3-(2, 4-Dichlorobenzylideneamino)-2-Methylquinazolin-4(3H)-One (3g): Yield 67% (acetone); m.p. 139°C. IR (KBr max in cm^{-1}): 612 (C-Br), 1286 (N-N), 1509 (C-N), 1573 (C=N), 1610 (C-C of aromatic ring), 1718 (C=O), 3133 (aromatic CH streching); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.06 (s, 3H, CH_3), 7.71-8.50 (m, 6H, Ar-H), 8.88 (s, 1H, N=CH of benzylideneamino); Anal. Calcd. For $C_{16}H_{10}BrCl_2N_3O$: C, 46.75; H, 2.45; N, 10.22; Found: C, 46.72; H, 2.42; N, 10.24%

6-Bromo-3-(4-(Dimethylamino) Benzylideneamino)-2-Methylquinazolin-4(3H)-One (3h): Yield 65% (ethanol); m.p.145°C. IR (KBr max in cm^{-1}): 614 (C-Br), 1284 (N-N), 1508 (C-N), 1575 (C=N), 1615 (C-C of aromatic ring), 1716 (C=O), 3137 (aromatic CH streching); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.09 (s, 3H, CH_3), 2.94 (s, 6H, $N(CH_3)_2$), 7.70-8.50 (m, 7H, Ar-H), 8.84 (s, 1H, N=CH of benzylideneamino); Anal. Calcd. For $C_{18}H_{17}BrN_4O$: C, 56.12; H, 4.45; N, 14.54; Found: C, 56.15; H, 4.47; N, 14.56%

General Procedure for Preparation of 6-Bromo-3-(3-Chloro-2-(Substitutedphenyl)-4-Oxoazetidin-1-yl)-2-Methylquinazolin-4(3h)-One (4a-4h): A mixture of 3a-3h (0.3 mol), dry dioxane (5 ml) and triethylamine (0.6 mol) were taking in a conical flask. The reaction mixtures were stirred on an ice bath and when the temperature dropped below 5°C and then chloroacetylchloride (0.015 mol) was added dropwise with stirring. After completion of addition the stirring was comtinued for 10 hr at room temperature. The reaction mixtures were kept a side for 52 hr. Finally, the reaction masses were added to ice cold water to obtain the final product. It was filtered, washed with water, Dried and recryatallized from appropriate solvents to yield compounds (4a-4h).

6-Bromo-3-(3-Chloro-2-Phenyl-4-Oxoazetidin-1-yl)-2-Methylquinazolin-4(3H)-One (4a): Yield 64% (ethanol); m.p. 158°C. IR (KBr max in cm^{-1}): 613 (C-Br), 1282 (N-N), 1504 (C-N), 1573 (C=N), 1613 (C-C of aromatic ring), 1713 (C=O), 3134 (aromatic CH streching); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.03 (s, 3H, CH_3), 3.77 (d, 1H, CH-Cl), 7.71-8.51 (m, 8H, Ar-H), 6.87 (d, 1H, N-CH of oxoazetidine); Anal. Calcd. For $C_{18}H_{13}BrClN_3O_2$: C, 51.64; H, 3.13; N, 10.04; Found: C, 51.65; H, 3.16; N, 10.06%

6-Bromo-3-(3-Chloro-2-(2-Hydroxyphenyl)-4-Oxoazetidin-1-yl)-2-Methylquinazolin-4(3H)-One (4b): Yield 62% (methanol); m.p. 160°C. IR (KBr max in cm^{-1}): 611 (C-Br), 1285 (N-N), 1507 (C-N), 1572 (C=N), 1610 (C-C of aromatic ring), 1714 (C=O), 3136 (aromatic CH streching), 3451 (OH); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.07 (s, 3H, CH_3), 3.76 (d, 1H, CH-Cl), 6.85 (d, 1H, N-CH of oxoazetidine); 7.71-8.52 (m, 7H, Ar-H), 11.02 (s, 1H, OH exchangeable with D_2O); Anal. Calcd. For $C_{18}H_{13}BrClN_3O_3$: C, 49.74; H, 3.01; N, 9.67; Found: C, 49.75; H, 3.03; N, 9.64%

6-Bromo-3-(3-Chloro-2-(4-Methoxyphenyl)-4-Oxoazetidin-1-yl)-2-Methylquinazolin-4(3h)-One (4c): Yield 61% (acetone); m.p. 167°C. IR (KBr max in cm^{-1}): 610 (C-Br), 1225 (OCH_3), 1284 (N-N), 1508 (C-N), 1570 (C=N), 1610 (C-C of aromatic ring), 1715 (C=O), 3133 (aromatic CH streching); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.05 (s, 3H, CH_3), 3.39 (s, 3H, OCH_3), 3.74 (d, 1H, CH-Cl), 6.84 (d, 1H, N-CH of oxoazetidine); 7.70-8.52 (m, 7H, Ar-H), Anal. Calcd. For $C_{19}H_{15}BrClN_3O_3$: C, 50.86; H, 3.37; N, 9.36; Found: C, 50.85; H, 3.36; N, 9.38%

6-Bromo-3-(3-Chloro-2-(4-Hydroxy-3-Methoxyphenyl)-4-Oxoazetidin-1-yl)-2-Methylquinazolin-4(3h)-One (4d): Yield 59% (methanol); m.p. 170°C. IR (KBr max in cm^{-1}): 612 (C-Br), 1224 (OCH_3), 1287 (N-N), 1509 (C-N), 1573 (C=N), 1612 (C-C of aromatic ring), 1717 (C=O), 3137 (aromatic CH streching), 3452 (OH); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.06 (s, 3H, CH_3), 3.36 (s, 3H, OCH_3), 3.78 (d, 1H, CH-Cl), 6.83 (d, 1H, N-CH of oxoazetidine). 7.71-8.51 (m, 6H, Ar-H), 11.02 (s, 1H, OH exchangeable with D_2O); Anal. Calcd. For $C_{19}H_{15}BrClN_3O_4$: C, 49.11; H, 3.25; N, 9.04; Found: C, 49.15; H, 3.27; N, 9.06%

6-Bromo-3-(3-Chloro-2-(2-Chlorophenyl)-4-Oxoazetidin-1-yl)-2-Methylquinazolin-4(3h)-One (4e): Yield 57% (acetone); m.p. 178°C. IR (KBr max in cm^{-1}): 615 (C-Br), 1285 (N-N), 1503 (C-N), 1575 (C=N), 1616 (C-C of aromatic ring), 1714 (C=O), 3138 (aromatic CH streching); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.03 (s, 3H, CH_3), 3.75 (d, 1H, CH-Cl), 6.87 (d, 1H, N-CH of oxoazetidine); 7.72-8.52 (m, 7H, Ar-H), Anal. Calcd. For $C_{18}H_{12}BrCl_2N_3O_2$: C, 47.71; H, 2.67; N, 9.27; Found: C, 47.75; H, 2.69; N, 9.26%

6-Bromo-3-(3-Chloro-2-(4-Chlorophenyl)-4-Oxoazetidin-1-yl)-2-Methylquinazolin-4(3h)-One (4f): Yield 54% (ethanol); m.p. 183°C. IR (KBr max in cm^{-1}): 610 (C-Br), 1282 (N-N), 1504 (C-N), 1571 (C=N), 1610 (C-C of aromatic ring), 1716 (C=O), 3133 (aromatic CH streching); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.04 (s, 3H, CH_3), 3.74 (d, 1H, CH-Cl), 6.88 (d, 1H, N-CH of oxoazetidine); 7.71-8.50 (m, 7H, Ar-H), Anal. Calcd. For $C_{18}H_{12}BrCl_2N_3O_2$: C, 47.71; H, 2.67; N, 9.27; Found: C, 47.72; H, 2.69; N, 9.28%

6-Bromo-3-(3-Chloro-2-(2, 4-Dichlorophenyl)-4-Oxoazetidin-1-yl)-2-Methylquinazolin-4(3h)-One (4g): Yield 53% (ethanol); m.p. 189°C. IR (KBr max in cm^{-1}): 612 (C-Br), 1281 (N-N), 1509 (C-N), 1573 (C=N), 1613 (C-C of aromatic ring), 1718 (C=O), 3135 (aromatic CH streching); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.09 (s, 3H, CH_3), 3.76 (d, 1H, CH-Cl), 6.87 (d, 1H, N-CH of oxoazetidine); 7.70-8.52 (m, 6H, Ar-H), Anal. Calcd. For $C_{18}H_{11}BrCl_3N_3O_2$: C, 44.34; H, 2.27; N, 8.62; Found: C, 44.35; H, 2.29; N, 8.64%

6-Bromo-3-(3-Chloro-2-(4-(Dimethylamino) Phenyl)-4-Oxoazetidin-1-yl)-2-Methylquinazolin-4(3h)-One (4h): Yield 51% (methanol); m.p. 192°C. IR (KBr max in cm^{-1}): 611 (C-Br), 1284 (N-N), 1508 (C-N), 1571 (C=N), 1610 (C-C of aromatic ring), 1715 (C=O), 3133 (aromatic CH streching); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.07 (s, 3H, CH_3), 2.97 (s, 6H, $N(CH_3)_2$), 3.77 (d, 1H, CH-Cl), 6.85 (d, 1H, N-CH of oxoazetidine); 7.71-8.53 (m, 7H, Ar-H), Anal. Calcd. For $C_{20}H_{18}BrClN_4O_2$: C, 52.02; H, 3.93; N, 12.13; Found: C, 52.05; H, 3.94; N, 12.16%

General Procedure for Preparation of 3-(6-Bromo-2-Methyl-4-Oxoquinazolin-3(4h)-yl)-2-(Substitutedphenyl) Thiazolidin-4-One (5a-5h): To ethanolic solution (60 ml) of compounds (3a-3h) (0.03 mol) thioglycolic acid (0.04 mol) was added in the presence of anhydrous zinc chloride. The reaction mixtures were refluxed for 10 hr. The excess of solvent was distilled off and separated masses were poured in to ice water, filtered and washed with water and recrystallized from suitable solvents to give compounds 5a-5h.

3-(6-Bromo-2-Methyl-4-Oxoquinazolin-3(4h)-yl)-2-(Substitutedphenyl) Thiazolidin-4-One (5a): Yield 50% (ethanol); m.p. 195°C. IR (KBr max in cm^{-1}): 614 (C-Br), 749 (C-S-C of thiazole),1283 (N-N), 1503 (C-N), 1571 (C=N), 1612 (C-C of aromatic ring), 1718 (C=O), 3136 (aromatic CH streching); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.07 (s, 3H, CH_3), 3.74 (s, 2H, CH_2 of oxothiazole), 7.71-8.52 (m, 8H, Ar-H), 8.85 (s, 1H, N-CH of thiazole); Anal. Calcd. For $C_{18}H_{14}BrN_3O_2S$: C, 51.93; H, 3.39; N, 10.09; Found: C, 51.95; H, 3.36; N, 10.06%

3-(6-Bromo-2-Methyl-4-Oxoquinazolin-3(4h)-yl)-2-(Substitutedphenyl) Thiazolidin-4-One (5b): Yield 59% (acetone); m.p. 205°C. IR (KBr max in cm^{-1}): 616 (C-Br), 748 (C-S-C of thiazole),1287 (N-N), 1506 (C-N), 1573 (C=N), 1615 (C-C of aromatic ring), 1719 (C=O), 3138 (aromatic CH streching), 3450 (OH); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.03 (s, 3H, CH_3), 3.77 (s, 2H, CH_2 of oxothiazole), 7.70-8.51 (m, 7H, Ar-H), 8.85 (s, 1H, N-CH of thiazole), 11.04 (s, 1H, OH exchangeable with D_2O); Anal. Calcd. For $C_{18}H_{14}BrN_3O_3S$: C, 50.01; H, 3.26; N, 9.72; Found: C, 50.03; H, 3.24; N, 9.76%

3-(6-Bromo-2-Methyl-4-Oxoquinazolin-3(4h)-yl)-2-(Substitutedphenyl) Thiazolidin-4-one (5c): Yield 47% (ethanol); m.p. 202°C. IR (KBr max in cm^{-1}): 614 (C-Br), 749 (C-S-C of thiazole), 1228 (OCH_3), 1282 (N-N), 1505 (C-N), 1572 (C=N), 1611 (C-C of aromatic ring), 1713 (C=O), 3139 (aromatic CH streching); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.05 (s, 3H, CH_3), 3.39 (s, 3H, OCH_3), 3.76 (s, 2H, CH_2 of oxothiazole), 7.71-8.50 (m, 7H, Ar-H), 8.87 (s, 1H, N-CH of thiazole); Anal. Calcd. For $C_{19}H_{16}BrN_3O_3S$: C, 51.13; H, 3.61; N, 9.41; Found: C, 51.15; H, 3.64; N, 9.43%

3-(6-Bromo-2-Methyl-4-Oxoquinazolin-3(4h)-yl)-2-(Substitutedphenyl) Thiazolidin-4-One (5d): Yield 45% (methanol); m.p. 209°C. IR (KBr max in cm^{-1}): 610 (C-Br), 748 (C-S-C of thiazole),1228 (OCH_3), 1284 (N-N), 1508 (C-N), 1570 (C=N), 1610 (C-C of aromatic ring), 1715 (C=O), 3133 (aromatic CH streching), 3450 (OH); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.05 (s, 3H, CH_3), 3.37 (s, 3H, OCH_3), 3.75 (s, 2H, CH_2 of oxothiazole), 7.72-8.51 (m, 6H, Ar-H), 8.86 (s, 1H, N-CH of thiazole), 11.02 (s, 1H, OH exchangeable with D_2O); Anal. Calcd. For $C_{19}H_{16}BrN_3O_4S$: C, 49.36; H, 3.49; N, 9.09; Found: C, 49.35; H, 3.46; N, 9.06%

3-(6-Bromo-2-Methyl-4-Oxoquinazolin-3(4h)-yl)-2-(Substitutedphenyl) Thiazolidin-4-One (5e): Yield 43% (acetone); m.p. 190°C. IR (KBr max in cm^{-1}): 613 (C-Br), 712 (C-Cl), 745 (C-S-C of thiazole), 1286 (N-N), 1509 (C-N), 1575 (C=N), 1613 (C-C of aromatic ring), 1719 (C=O), 3135 (aromatic CH streching); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.07 (s, 3H, CH_3), 3.74 (s, 2H, CH_2 of oxothiazole), 7.71-8.52 (m, 7H, Ar-H), 8.85 (s, 1H, N-CH of thiazole); Anal. Calcd. For $C_{18}H_{13}BrClN_3O_2S$: C, 47.96; H, 2.91; N, 9.32; Found: C, 47.95; H, 2.94; N, 9.36%

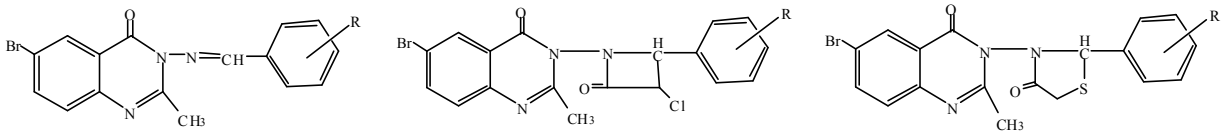
3-(6-Bromo-2-Methyl-4-Oxoquinazolin-3(4h)-yl)-2-(Substitutedphenyl) Thiazolidin-4-One (5f): Yield 42% (ethanol); m.p. 198°C. IR (KBr max in cm^{-1}): 614 (C-Br), 713 (C-Cl), 745 (C-S-C of thiazole), 1283 (N-N), 1507 (C-N), 1571 (C=N), 1611 (C-C of aromatic ring), 1716 (C=O), 3134 (aromatic CH streching); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.06 (s, 3H, CH_3), 3.72 (s, 2H, CH_2 of oxothiazole), 7.71-8.50 (m, 8H, Ar-H), 8.84 (s, 1H, N-CH of thiazole); Anal. Calcd. For $C_{18}H_{13}BrClN_3O_2S$: C, 47.96; H, 2.91; N, 9.32; Found: C, 47.93; H, 2.95; N, 9.35%

3-(6-Bromo-2-Methyl-4-Oxoquinazolin-3(4h)-yl)-2-(Substitutedphenyl) Thiazolidin-4-One (5g): Yield 41% (methanol); m.p. 196°C. IR (Kbr max in cm^{-1}): 610 (C-Br), 715 (C-Cl), 748 (C-S-C of thiazole), 1284 (N-N), 1508 (C-N), 1570 (C=N), 1610 (C-C of aromatic ring), 1715 (C=O), 3133 (aromatic CH streching); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.05 (s, 3H, CH_3), 3.73 (s, 2H, CH_2 of oxothiazole), 7.70-8.51 (m, 6H, Ar-H), 8.87 (s, 1H, N-CH of thiazole); Anal. Calcd. For $C_{18}H_{12}BrCl_2N_3O_2S$: C, 44.56; H, 2.49; N, 8.66; Found: C, 44.55; H, 2.47; N, 8.68%

3-(6-Bromo-2-Methyl-4-Oxoquinazolin-3(4h)-yl)-2-(Substitutedphenyl) Thiazolidin-4-One (5h): Yield 40% (ethanol); m.p. 220°C. IR (KBr max in cm^{-1}): 612 (C-Br), 746 (C-S-C of thiazole), 1286 (N-N), 1507 (C-N), 1572 (C=N), 1611 (C-C of aromatic ring), 1714 (C=O), 3132 (aromatic CH streching); ^{1}HNMR ($CDCl_3$ + DMSO-d_6) & in ppm: 2.07 (s, 3H, CH_3), 2.97 (s, 6H, $N(CH_3)_2$), 3.74 (s, 2H, CH_2 of oxothiazole), 7.71-8.52 (m, 7H, Ar-H), 8.85 (s, 1H, N-CH of thiazole); Anal. Calcd. For $C_{20}H_{19}BrN_4O_2S$: C, 52.29; H, 4.17; N, 12.20; Found: C, 52.25; H, 4.19; N, 12.23%

Antifungal Activity: All the newly synthesized compounds and the standard drug, fluconazole were tested for their antifungal activity by employing the standard agar disc diffusion method [15]. The following strains of fungi have been used in this study: Aspergillus fumigatus, Candida albicans, Candida albicans ATCC 10231 and Candida Krusei G03. All cultures were maintained on [Sabouraud-dextrose agar] SDA and incubated at 30°C. To prepare homogeneous suspensions of the above mentioned fungi for the disc assays, they were grown in Sabouraud broth, centrifuged to collect the pellet and buffered with saline. The fungal pellet was homogenized in a sterile hand-held homogenizer. This suspension was then plated onto SDA using a fungal spreader to obtain an even growth field. Sterile 6 mm Whatmann filter paper was impregnated with 250 μg/mL concentration of the various test compounds and standard drug fluconazole. These discs were then placed in the center of each quadrant of an SDA plate. Each plate had one control disc impregnated with DMSO. The plates were incubated at 30°C. After 48 h, the plates were removed.

RESULT AND DISCUSSION



(3a-3h) (4a-4h) (5a-5h)

Antifungal activity of compounds 3a-3h, 4a-4h and 5a-5h

Table 1:

Comp.No.	R	Fungal growth inhibition(diameter)			
		A. fumigates	C. albicans	C. albicansATCC	C. krusai
3a	H	8mm	-	7mm	-
3b	2-OH	9mm	-	8mm	-
3c	4-OCH_3	7mm	-	-	8mm
3d	4-OH,3-OCH_3	-	8mm	-	-
3e	2-Cl	8mm	-	10mm	9mm
3f	4-Cl	10mm	9mm		10mm
3g	2,4-Cl	13mm	11mm	-	15mm
3h	4-$N(CH_3)_2$	10mm	-	12mm	12mm
4a	H	-	11mm	-	13mm
4b	2-OH	14mm	-	15mm	-
4c	4-OCH_3	15mm	17mm	16mm	-
4d	4-OH,3-OCH_3	-	19mm	-	16mm
4e	2-Cl	16mm	-	21mm	18mm
4f	4-Cl	20mm	17mm	18mm	-
4g	2,4-Cl	24mm	28mm	24mm	19mm
4h	4-$N(CH_3)_2$	-	23mm	25mm	-
5a	H	20mm	-	21mm	-
5b	2-OH	22mm	27mm	24mm	18mm
5c	4-OCH_3	-	22mm	-	20mm
5d	4-OH,3-OCH_3	21mm	-	23mm	-
5e	2-Cl	22mm	23mm	-	-
5f	4-Cl	-	30mm	24mm	19mm
5g	2,4-Cl	24mm	32mm	26mm	20mm
5h	4-$N(CH_3)_2$	23mm	28mm	25mm	-
	fluconazol		29mm	25mm	19mm

All the newly synthesized compounds were reported in table 1 were tested in vitro for their antifungal activity against various fungi. Compounds 3a-3h showed moderate antifungal activity. On the cyclisation of compounds 3a-3h with chloroacetic chloride and thioglycolic acid yielded compounds 4a-4h and 5a-5h respectively. Antifungal activity was increase due to presence of azetidinone and thiazolidinone ring. Among the compounds 4a-4h and 5a-5h, compounds 4g, 4h, 5b, 5f, 5g and 5h showed good antifungal activity and rest compounds showed less activity against different fungi. Compound 5g was more potent compared with standard drug fluconazole.

CONCLUSION

Antifungal activity results indicated that all the derivatives of quinazolinones showed antifungal activity. Moreover, compounds 5a-5h containing thiazolidinone ring exhibited better antifungal activity than compounds 4a-4h having azetidinone ring. Para chlorophenyl substituted quinazolinone derivatives showed more efficiency due to presence of more electronegative atom.

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