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Synthesis and antifungal activity of newer substituted Quinazolinones

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Abstract: 3-(2'-substitutedarylidineimino-1',3'-thiazol-4'-yl)amino-2-methyl-monosubstituted quinazolin-4(3H)-ones (4a-d), 3-[2'-(3'-chloro-2'-oxo-4'-substitutedaryl-1'-zetidinyl)-1'-,3'-thiazol-4'-yl]-amino-2- methylmono substituted quinazolin-4-(3H)-ones (5a-d), and 3-[2'-(substitutedaryl-4'-thiazolidinon-3'-yl)-1',3'-thiazol-4'-yl]-amino-2-methylmono substitutedquinazolin-4(3H)-ones (6a-d) were synthesized in present study. All the compounds have been screened for their anti-fungal activity. The structure of all by compounds was confirmed by their analytical(C, H, N) and spectral (IR, 1H NMR) data.

Key words: Synthesis of newer substituted Quinazolinones, antifungal activity.

Introduction

Quinazolinones are the versatile nitrogen containing heterocyclic compounds displaying a wide variety of biological and pharmacological activities like anticonvulant[1], anti-inflammatory[2-3], antibacterial[4-5] and antifungal[6-10]. The chemistry and pharmacology of quinazolinone have been of great interest to medicinal chemistry. In 1985, Weddige synthesized the first quinazolinone and named it anhydroformy lamidobenzamide Later on extensive work on this nucleus was done, further for care of humans suffering from different diseases many drugs incorporating this nucleus were developed. Recently, several scientists have elucidated that quinazolinone system possess the various variable sites like position 2 and 3, which can be suitable modified by the introduction of various heterocyclic moieties to yield the potent antifungal agents. Various derivatives of quinazolinone have been synthesized and evaluated for their antifungal activity.

Results

Chemistry

Compound 1a-b on treatment with chloroacetyl chloride afforded compound. Compound 2a-b on reaction with thiourea gave 3-(2'amino-1,3'-thiazol-4'-yl)amino-2 methyl monosubstituted quinazolin-4(3H)-ones 3a-b, further compound 3a-b was reacted with different aromatic aldehydes to gives 3-[2'-substitutedaryl-ideneimino-1',3'-thiazol-4'-yl)amino-2-methylmonosubstituted quinazolin-4(3H)-ones (4a-4n). 3-[2'-(3"-chloro-2"-oxo-4"-substitutedaryl-1"-azetidinyl)-1',3'-thiazol-4'-yl]amino-2-methy monosubstituted quinazolin-4(3H)-nes (5a-5n) were prepared from compound 4a-4n on treatment with triethyl amine and chloroacetyl chloride. On reacting with thioglycolic acid and anhydrous $ZnCl_2$ various substituted arylidene congeners (4a-4n) were cyclized to furnish 3-[2'-(2"-substituted aryl-4"-thiazolidin-3"-yl)-1',3'-thiazol-4'-yl]amino-2-methylmonosubstitutedquinazolin-4(3H)-ones (6a-6n). The structure of all by compounds was confirmed by their analytical(C, H, N) and spectral (IR, 1H NMR) data. The All the compounds have been screened for their anti-fungal activity.

Discussion

All the synthesized compounds i.e. **3a-3n, 4a-4n,** and **5a-5n** as well as standard drugs fluconazole and griseofulvin, were evaluated for antifungal activity against five strains of Candida species i.e. C.albicans, C.albicans ATCC, C.krusei G03, C.glabrata H05, and C.parapsilosis 22019, and three strains of Aspergillus species i.e. A. fumigatus, A.niger, and A.flavus at a concentration of 100mg/lt. The results are given in Table I. The results indicated that all the compounds possessed antifungal activity against one or the other fungal strains used. Among all the tested compounds, only compound **5d** revealed better antifungal activity than the standard against C.albicans, C.albicans ATCC, C.parapsilosis 22019, A.niger, and A.flavus, however it was found to be equipotent to one of the standard drug i.e. fluconazole against C.glabrata H05. Compound **51** was found to be almost equipotent to the standard drugs against C.albicans, C.albicans ATCC, C.parapsilosis 22019, A.niger, and A.flavus. (TableI).

TABLE I: Pharmacological data of compounds 4a-4n, 5a-5n and 6a-6n.

Antifungal activity # [diameter of inhibition zone (mm)]						Antifungal activity # [diameter of inhibition zone (mm)]		
Compounds	**Candida albicans**	**Candida albicans ATCC**	**Candida Krusei GO3**	**Candida glabrata HO5**	**Candida parapsiolsis 22019**	**Aspergillus Fumigatus**	**Aspergillus niger**	**Aspergillus Flavus**
@ Control	0	0	0	0	0	0	0	0
Fluconazole*	29	25	19	15	20	-	90	84
Griseofulvin*	25	26	18	16	22	80	88	82
4a	5	-	-	-	-	-	-	-
4b	8	-	-	-	8	-	24	-
4c	10	-	-	-	9	-	25	-
4d	13	13	-	-	11	-	34	25
4e	8	-	-	-	7	-	20	-
4f	9	8	-	-	8	-	29	18
4g	-	-	-	4	8	-	-	-
4h	-	-	-	5	9	-	26	-
4i	-	-	-	-	-	-	22	-
4j	-	-	-	6	-	-	28	-
4k	9	9	-	-	7	-	20	15
4l	10	11	-	-	9	-	27	18
4m	7	6	-	-	5	-	17	-
4n	8	9	-	-	7	-	24	-
5a	8	-	-	-	9	-	28	-
5b	12	10	-	6	-	-	30	-
5c	18	16	-	-	-	-	48	-
5d	20	18	-	-	14	-	80	76
5e	14	12	-	-	-	30	40	-
5f	18	15	-	-	10	-	70	65
5g	-	-	-	6	10	-	-	-
5h	-	12	-	11	11	-	40	-
5i	5	9	-	-	-	-	35	-
5j	9	11	-	8	-	-	40	-
5k	12	11	-	-	10	-	50	30
5l	13	14	-	-	12	-	62	40
5m	10	9	-	-	-	-	46	-
5n	11	10	-	-	5	-	54	-
6a	15	-	-	-	12	-	48	46
6b	18	14	-	9	-	-	52	50
6c	20	20	8	12	18	32	80	62
6d	34	30	12	15	28	70	96	88
6e	17	16	-	6	14	-	52	42
6f	22	23	-	9	20	-	66	72
6g	-	9	-	5	12	-	50	-
6h	-	12	-	7	12	56	58	48
6i	10	16	-	-	-	-	-	48
6j	20	18	-	11	-	64	64	52

6k	20	18	5	-	13	-	68	66
6l	24	24	7	-	19	-	87	82
6m	16	13	-	-	8	-	60	58
6n	18	16	-	-	10	-	72	70

\# Concentration was 100 mg/Lt.
@ 10% DMSO is methanol
-: No inhibition zone
* Standard drugs used for comparison

Biological Section

Newer synthesized compounds have been screened for their antifungal activity. Antifungal activity was performed against Aspergillus Fumigatus, Aspergillus niger, Aspergillus Flavus, Candida albicans, Candida albicans ATCC, Candida Krusei GO3, Candida glabrata HO5, Candida parapsiolsis 22019 using Fluconazole as standard drug.

Antifungal activity

Poisened Food Technique (Gehlot and Vohra, 1998) was performed to evaluate the antifungal property of the test compounds and standard drugs i.e. fluconazole and griseofulvin against Aspergillus flavus, A. niger and A. Fumigatus.

10% solution of DMSO in methanol was prepared , 100 mg of test compound as well as the reference drugs were dissolved in sufficient amount of this solution (5 ml). This solution (5 ml) was added to 995 ml Czapex Dox Agar medium so as to obtained 100 ml/L concentration of the compound in the medium. 5 ml of 10% DMSO in methanol solution (without any test compound and standard drugs) added to the 995 ml Czapex Dox Agar mediumserved as control. The resultanat solution were thoroughly mixed and approximately 20 ml of the solution was poured into 9 cm sterile glass petridishes and allowed to set. The resulting agar plates were inoculated with 5mm plugs of fungal mycelia cut from freshly prepared, actively growing cultures. The plates were then incubated at 25± C in the dark for eight days. The diameters of each colony was measured after eight days of incubation. Three replicates were taken for each test compound and for each organism test cultures. The average inhibition due to the given test compound was calculated using the equation:

Inhibition % = (C-T) x 100 / C

Wherein:-

C=Diameter of the fungal colony in mm in the control medium.

T=Diameter of the fungal colony in mm in the test medium,containing the given test compound or the reference drugs.

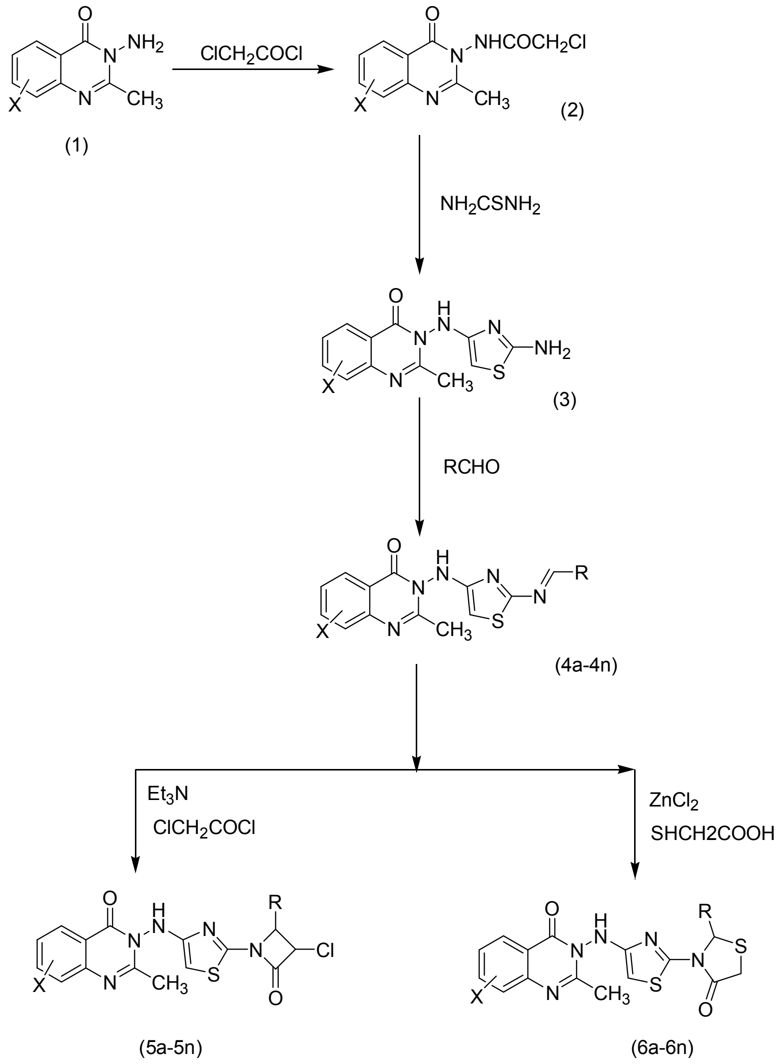
Standard Agar Disc Diffusion Method (Pai and Platt, 1995)

All the cultures were maintained of Sabouraud Dextrore Agar medium and incubatef at 30 C. In order to prepare homogenous suspension of these fungi for disc assays, they were grown overnight in Sabouraud broth, centrifuged to collect the pellet and resuspended in sterile phosphate buffered saline. The fungal pellet was homogenized in sterile hand held homogenizer. This suspension was then plated on a Sabouraud Dextrose Agar medium using a bacterial spreaded to obtain an even growth. Sterile 6 mm whattmann filter paper disc were impregnated with 100 mg / L of various test compounds and standard drugs. These discs were then placed in the centre of quadrent of Sabauroud Dextrose Agar medium plate. These plates and one control disc impregnated with 10 % DMSO in methanol. These plates were incubated at 30 C. Three replicates were used for each test compound as well as for each standard drug used. After 48 hours the plates were removed and radii of inhibition zone were measured and the average calculated.

Conclusion:

From the above results and discussion following conclusion can be drawn:

- Substituted arylidine congeners (**3a-3n**) introduces antifungal activity in the compounds.
- Presence of azetidinone ring in the compounds enhances the antifungal activity.
- Presence of thiazolidinone ring in the compounds enhances the antifungal activity to a considerable level.
- Compounds with phenyl ring having hydroxy group or methoxy group at ortho or para position exhibit prominent antifungal activity. Ortho derivatives possess the better antifungal activities.
- Presence of bromo group at 6 position of quinazolinone nuclei actively participates in increasing the antifungal activity of the compounds.



Scheme-1

Chemistry

Experimental

The melting points of the compounds were determined in open capillaries with the help of thermonic melting point apparatus and were uncorrected. The homogeneity of all the newly synthesized compounds was routinely checked by thin layer chromatography on Silica gel G plates of 0.5 mm thickness, eluent was the mixture of different polar and nonpolar solvent in varying proportions and spots were located by using UV (254 nm) and iodine chamber.

Elemental analysis (C,H,N) of all the compounds were determined through Carlo-Erba 1108 elemental analyzer and results were found within ± 0.4% of theoretical values. Infra red (IR) spectra were recorded in KBr on Bruker IFS-66V FI-IR instrument and V_{max} was recorded in cm^{-1}. ^1H NMR spectra were recorded by Brucker DRX-400 FTNMR instrument using $CDCl_3$ or $DMSOd_6$ as solvent and tetramethylsilane (TMS) as internal reference standard. Chemical shift value was recorded as δ (ppm). Mass spectra were determined on mass spectrum EI instrument.

3-Chloroacetyl amino-2-methyl-6-monosubstituted quinazolin-4(3H)-ones (2)

A mixture of compound 1 i.e. 3-amino-2-methylmono substitutedquinazolinones (0.01 mol), chloroacetyl chloride (0.01 mol) and anhydrous K_2CO_3 (5.00 gm) in acetone (dry, 80 ml were refluxed for 18-20 hours on a water bath. Acetone was distilled off and the remaining solid mass was poured into water, filtered and the separated out solid recrystallised to give the following compounds:

3-Chloroacetyl amino-2-methyl-quinazolin-4(3H)-one (2a)

M.P. 120°C; Yield 60%; Recrystallisation Solvent Methanol/Water; Spectral Analysis:IR (KBr) (cm^{-1}) : 780.81 (C-Cl), 1224.09 (C-N), 1552.03 (C-C of aromatic), 1681.55 (C=O), 2960.24 (CH_2), 3250.13 (NH). ^{1}H NMR ($CDCl_3$ + $DMSOd_6$) δ (ppm) : 2.15 (s, 3H, CH_3), 4.35 (s, 2H, $COCH_2$), 7.47-7.75 (, 4H, Ar-H) 8.80 (bs, 1H, NHCO). Molecular Formula $C_{11}H_{10}N_3O_2Cl$ Elemental analysis: C , Calculated 52.48;Found 52.20, H ,Calculated 3.97; Found 3.60; N ,Calculated 16.69;Found 16.91 MS : $[M]^+$ m/z 251.5

3-Chloroacetylamino-2-methyl-6-bromoquinazolin-4(3H)-one (2b)

M.P. 205°C; Yield 60%; Recrystallisation Solvent Methanol/Water; IR (KBr) (cm^{-1}) : 601 (C-Br), 782.56 (C-Cl), 1222.10 (C-N), 1558.05 (C-C of aromatic), 1677.32 (C=O), 2965.02 (CH_2), 3257.13 (NH). ^{1}H NMR ($CDCl_3$+$DMSOd_6$) δ (ppm) : 2.18 (s, 3H, CH_3), 4.32 (s, 2H, $COCH_2$), 7.40-7.72 (m, 3H, Ar-H), 8.82 (bs, 1H, NHCO).Molecular Formula $C_{11}H_9N_3O_2ClBr$, Elemental Analysis: C, Calculated 39.93; Found 39.54; H Calculated 2.72, Found 2.50; N Calculated 12.70; Found 12.92; MS : $[M]^+$ m/z 330.5

3-(2'amino-1,3'-thiazol-4'-yl)amino-2methyl monosubstituted quinazolin-4(3H)-ones (3)

A solution of compound 2 (0.01 mol) in absolute ethanol (200 ml) was treated with a solution of thiourea (0.02 mol). The reaction mixture was refluxed for 10-12 hours. The separated solid was filtered, washed with 2% $NaHCO_3$ solution, then with water, dried and recrystallised. The compounds thus formed are:

3-(2'-amino-1',3'-thiazol-4'-yl)amino-2-methyl-quinazolin-4(3H)-one (3a)

M.P. 145°C; Yield 57%; Recrystallisation Solvent Ethanol/Water; Spectral Analysis; IR (KBr) (cm^{-1}): 680.38 (C-S-C), 1520.22 (N-N), 1550.02 ((C-C of Aromatic), 1616.13 (C=N), 1685.12 (C=O), 2918.31 (methyl C-H stretch), 3050.36 (aromatic C-H), 3270.60 (NH_2), 3340.60 (N-H).^{1}H NMR ($CDCl_3$+$DMSOd_6$) δ (ppm) : 2.34 (s, 3H, CH_3), 7.40-7.84 (m, 5H, Ar-H), 7.75 (bs, 2H, NH_2, exchangeable with D_2O), 8.02 (s, 1H, thiazole CH), 12.50 (bs, 1H, NH). Molecular Formula $C_{12}H_{11}N_5OS$. Elemental Analysis: C Calculated 52.75; Found 52.54; H Calculated 4.03; Found 4.20; N Calculated 25.64; Found 25.81; MS: $[M]^+$ m/z 273.

3-(2'amino-1',3'-thiazol-4'-yl)amino-2-methyl-6-bromoquinazolin-4(3H)-one (3b)

M.P. 195°C; Yield 58%; Recrystallisation Solvent Ethanol/Water; Spectral Analysis: IR (KBr) (cm^{-1}) : 600.07 (C-Br), 683.76 (C-S-C), 1424.54 (C-N), 1524.13 (N-N), 1598.32 (C=C), 3325.53 (NH). ^{1}H NMR ($CDCl_3$+$DMSOd_6$) δ (ppm) : 2.30 (s, 3H, CH_3), 6.84-7.19 (m, 4H, Ar-H); Molecular Formula $C_{12}H_{10}N_5OSBr$. Elemental Analysis: C Calculated 40.90; Found 42.74; H Calculated 2.84; Found 2.70; N Calculated 19.88;Found 19.99; MS: $[M]^+$ m/z 352.

3-(2'substitutedbenzylidenimino-1'3'thiazol-4'-yl)amino-2-methylmono substituted quinazolin-4(3H)-ones (4).

Arylaldehyde (0.02 mol) and 2-3 drops of glacial acetic acid were added to a solution of compound 3 (0.01 mol) in ethanol (60 ml) and the resultant solution was refluxed for 16-18 hours. The solvent was distilled off and residue washed with petroleum ether (40°-60°) and recrystallised. Following compounds were synthesised

3-(2'-o-hydroxybenzylidenimino-1',3'thiazol-4'-yl)amino-2-methylquinazolin-4(3H)-one (4c)

M.P. 102°C; Yield 50%; Recrystallisation Solvent Methanol/Water; Spectral Analysis: IR (KBr) (cm^{-1}): 683.75 (C-S-C), 1520.32 (C-C of aromatic), 1635.09 (C=N), 1668.54 (C=O), 2920.34 (methyl C-H), 3045.65 (aromatic C-H), 3323.22 (-OH), 3342.82 (N-H). ^{1}H NMR ($CDCl_3$+$DMSOd_6$) δ (ppm) : 1.38 (m, 1H, CH), 2.15 (s, 3H, CH_3), 6.60-7.35 (m, 9H, Ar-H), 8.01 (s, 1H, thiazole CH), 8.25 (s, 1H, N=CH), 8.50 (s, 1H, CH-Ar), 12.00 (bs, 1H, NH, exchangeable with D_2O). Molecular Formula $C_{19}H_{15}N_5O_2S$. Elemental Analysis: C Calculated 60.47; Found 60.59; H Calculated 3.97; Found 4.09; N Calculated 18.56; Found 18.42; MS: $[M]^+$ m/z 377

3-(2'-o-hydroxybenzylidenimino-1',3',thiazol-4'-yl)amino-2-methyl-6-bromo quinazolin-4(3H)-one (4d)

M.P. 200°C; Yield 52%; Recrystallisation Solvent Methanol/Water; Spectral Analysis: IR (KBr) (cm^{-1}): 603.02 (C-Br), 681.87 (C-S-C), 1522.43 (C-O of aromatic), 1633.34 (C=N), 3325.84 (-OH), 3345.26 (N-H).b^{1}H NMR ($CDCl_3$+$DMSOd_6$) δ(ppm): 1.35 (m, 1H, CH), 210 (s, 3H, CH_3), 6.60-7.35 (m, 7H, Ar-H), 12.40 (ss, 1H, OH-Ar, exchangeable with D_2O). Molecular Formula $C_{19}H_{14}N_5O_2SBr$ .Elemental Analysis: C Calculated 50.00; Found 49.92; H Calculated 3.07; Found 3.29; N Calculated 15.35; Found 15.59; MS: $[M]^+$ m/z 456.

Other arylideneaminoquinazolinones have been synthesized following the same procedure as described above for 4c and 4d. Their physical and analytical data are given in Table II.

3-[2'-(3'-chloro-2'-oxo-4'-substitutedphenyl-1'azetidinyl)-1',3',thiazol-4'-yl]amino-2-methylmonosubstitutedquinazolin-4(3H)-ones (5)

To a solution of compound 4 (0.01 mol) in absolute ethanol (100 ml) 2-3 drops of trimethyl amine and chloroacetyl chloride (0.02 mol) were added drop by drop with one hour of constant stirring. The resulting mixture was stirred further for 2 hours and then refluxed for an hour, cooled and poured into ice. Solid thus obtained was filtered and recrystallised. The resulting compounds are as follows:

3-[2'(3'-chloro-2'-oxo-4'-o-hydroxyphenyl-1'-azetidinyl)-1',3'thiazol-4'-yl]amino-2-methylquinazolin-4(3H)-one (5c)

M.P. 120°C; Yield 45%; Recrystallisation Solvent Acetone/Petroleum ether; Spectral Analysis: IR (KBr) (cm^{-1}): 624.67 (C-Cl), 685.87 (C-S-C), 1284.44 (N-N), 1560.13 (C-C of aromatic), 1600.56 (C=N), 1744.05 (C=O of β-lactam), 1790.08 (C=O), 2920.63 (methyl C-H), 3053.25 (aromatic C-H), 3332.56 (N-H), 3474.81 (OH). ^{1}H NMR (CDCl$_3$+DMSOd$_6$) δ (ppm): 2.15 (s, 3H, CH$_3$), 4.65 (d, 1H, CH-Cl), 6.20 (s, 1H, N-CH-Ar), 8.00 (s, 1H thiazole CH), 7.15-8.80 (m, 9H, Ar-H) 12.42 (ss, 1H, OH exchangeable with D$_2$O). Molecular Formula $C_{21}H_{16}N_5O_3SCl$. Elemental Analysis: C Calculated 55.56; Found 55.81; H Calculated 3.53; Found 3.72; N Calculated15.44;Found 15.20 .MS: [M]$^+$ m/z (437.5).

3-[2'-(3'-chloro-2'-oxo-4'-o-hydroxyphenyl-1-azetidinyl)-1',3'thiazol-4'-yl]amino-2-methyl-6-bromoquinazolin-4(3H)-one (5d)

M.P. 246°C; Yield 46%; Recrystallisation Solvent Acetone/Petroleum ether; Spectral Analysis. IR (KBr) (cm^{-1}): 605.22 (C-Br), 620.82 (C-Cl), 1280.24 (N-N), 1420.62 (C-N), 1565.07 (C-C of aromatic), 1605.27 (C=N, 1742.98 (C=O of β-lactam), 1793 (C=O), 2922.66 (methyl C-H), 3050.56 (aromatic C-H), 3333.39 (N-H), 3472.06 (OH). ^{1}H NMR (CDCl$_3$+DMSOd$_6$) δ (ppm): 2.30 (s, 3H, CH$_3$), 4.62 (d, 1H, CH-Cl), 6.25 (s, 1H, N-CH-Ar), 7.10-8.85 (m, 8H, Ar-H), 8.05 (s, 1H, thiazole CH), 12.40 (ss, 1H, OH-Ar, exchangeable with D$_2$O). Molecular Formula $C_{21}H_{15}N_5O_3SClBr$ (516.5). C Calculated 47.32; Found 47.01; H Calculated 2.82; Found 2.51; N Calculated 13.14; Found 13.36 .MS : [M]$^+$ m/z 516.5

Other substitutedarylazetidinones were synthesized by employing the same method as discussed for 5c and 5d. Physical and analytical data of compounds 5a-5n are mentioned in Table II.

3-[2'-(2'-substituted-4'-substitutedphenyl-4'-thiazolidin-3'-yl)-1',3'thiazol-4'-yl]amino-2-methylmonosubstituted quinazolin-4(3H)-ones (6)

A stirred solution of compound 6 (0.01 mol) was refluxed in dry DMF (80 ml) containing a small amount of anhydrous ZnCl$_2$ and thioglycolic acid (0.02 mol) for 18 hours. The reaction mixture was cooled and poured into ice cold water. The separated solid was filtered, washed and recrytallised by using appropriate solvents to give the following compounds:

3-[2'-(2'-o-hydroxyphenyl-4'-thiazolidin-3'-yl) 1',3'thiazol-4'-yl]amino-2-methyl quinazolin-4(3H)-one (6c)

M.P. 110°C; Yield 46%; Recrystallisation Solvent Methanol/Water; Spectral Analysis: IR (KBr) (cm^{-1}): 682.37 (C-S-C), 1140.74 (C.S of β-thialactam), 1760.55 (C=O of β-thialactam), 1285.52 (N-N), 1423.10 (C-N), 1563.05 (C-C of aromatic), 1620.48 (C-N), 2919.43 (methyl C-H), 3040.20 (aromatic C-H), 3340.37 (N-H). ^{1}H NMR (CDCl$_3$+DMSOd$_6$) δ (ppm) : 2.17 (s, 3H, CH$_3$), 3.50 (s, 2H, CH$_2$ of β-thialactam), 6.18 (s, 1H, N-CH-Ar), 8.03 (s, 1H, thiazole CH), 7.20-6.85 (m, 8H, Ar-H), 12.40 (ss, 1H, OH-Ar, exchangeable with D$_2$O). Molecular Formula $C_{21}H_{17}N_5O_3S_2$ .Elemental Analysis: C Calculated 60.14; Found 60.00; H Calculated 4.05; Found 4.24; N Calculated 16.71; Found 16.52. MS : [M]$^+$ m/z 451.

3-[2'-(2'-o-hydroxyphenyl-4'-thiazolidin-3'-yl)-1',3'-thiazol-4'-yl]amino-2-methyl-6-bromoquinazolin-4 (3H)-one (6d)

M.P. 265°C; Yield 48%; Recrystallisation Solvent Methanol/Water; Spectral Analysis: IR (KBr) (cm^{-1}): 610 (C-Br), 685 (C-S-C), 1143 (C-S of β-thialactam), 1764 (C=O of β-thialactam), 1287 (N-N), 1428 (C=N), 1560 (C-C of aromatic), 1624 (C=N), 2915 (methyl C-H), 3339 (N-H). ^{1}H NMR (CDCl$_3$+DMSOd$_6$) δ (ppm) : 2.15 (s, 3H, CH$_3$), 3.53 (s, 2H, CH$_2$ of β-thialactam), 6.15 (s, 1H, N-CH-Ar), 8.00 (s, 1H, thiazole CH), 7.15-6.80 (m, 7H, Ar-H), 12.43 (ss, 1H, OH-Ar, exchangeable with D$_2$O). Molecular Formula $C_{21}H_{15}N_5O_3S_2Br$ (530). Elemental Analysis: C Calculated 50.60; Found 50.78; H Calculated 3.01; Found 3.31; N Calculated 13.20; Found 13.00. MS : [M]$^+$ m/z 530.

Other substitutedarylthiazolidinones were prepared by the same method as described above for compounds 6c and 6d. Physical and analytical data of compounds 6a-6n are given in Table II.

Table II : Physical and analytical data of compounds 4a-4n, 5a-5n and 6a-6n.

Compd No.	X	R	M.P. (°C)	Yield (%)	Recrystallization solvent	Molecular Formula	Elemental analysis		
							%C Calcd. (Found)	% H Calcd. (Found)	% N Calcd. (Found)
4a	H	H	102	56	DMF	$C_{19}H_{15}N_5OS$	63.15 (63.01)	4.15 (4.27)	19.39 (19.17)
4b	6-Br	H	195	52	DMF	$C_{19}H_{14}N_5OSBr$	51.81 (52.04)	3.18 (3.10)	15.90 (16.12)
4c	H	o-OH	102	50	Methanol/Water	$C_{19}H_{15}N_5O_2S$	60.47(60.59)	3.97 (4.09)	18.56 (18.42)
4d	6-Br	o-OH	200	52	Methanol/Water	$C_{19}H_{14}N_5O_2SBr$	50.00 (49.92)	3.07 (3.29)	15.35 (15.59)
4e	H	p-OH	104	54	DMF	$C_{19}H_{15}N_5O_2S$	60.47 (60.59)	3.97 (3.75)	18.56 (18.40)
4f	6-Br	p-OH	205	52	DMF	$C_{19}H_{15}N_5O_2SBr$	50.00 (50.28)	3.07 (3.25)	15.35 (15.12)
4g	H	p-N$(CH_3)_2$	97	50	Ethanol/ Water	$C_{21}H_{20}ON_6S$	62.37 (62.09)	4.95 (4.70)	20.79 (20.50)
4h	6-Br	p-N$(CH_3)_2$	190	49	Ethanol/ Water	$C_{21}H_{19}ON_6S$	52.17 (52.26)	3.93 (3.80)	17.39 (17.10)
4i	H	m-OCH_3, p-OH	105	53	Methanol/Water	$C_{20}H_{17}O_3N_5S$	58.96 (59.17)	4.17 (4.25)	17.19 (17.10)
4j	6-Br	m-OCH_3, p-OH	205	50	Methanol/Water	$C_{20}H_{16}O_3N_5SBr$	49.38 (49.52)	3.29 (3.15)	14.40 (14.52)
4k	H	o-OCH_3	160	53	Ethanol/ Water	$C_{20}H_{17}O_2N_5S$	61.38 (61.55)	4.34 (4.12)	17.64 (17.50)
4l	6-Br	o-OCH_3	205	55	Ethanol/ Water	$C_{20}H_{16}O_2N_5SBr$	51.06 (51.20)	3.40 (3.22)	14.89 (15.00)
4m	H	p-OCH_3	180	54	Methanol/Water	$C_{20}H_{17}O_2N_5S$	61.38 (61.14)	4.34 (4.58)	17.64 (17.48)
4n	6-Br	p-OCH_3	220	60	Methanol/Water	$C_{20}H_{16}O_2N_5SBr$	51.06 (51.28)	3.40 (3.20)	14.89 (15.15)
5a	H	H	97	48	Methanol/Water	$C_{21}H_{16}N_5O_2SCl$	57.60 (57.92)	3.65 (3.37)	16.00 (16.18)
5b	6-Br	H	210	46	Methanol/Water	$C_{21}H_{15}N_5O_2SClBr$	48.78 (48.43)	2.90 (3.10)	13.55 (13.40)
5c	H	o-OH	120	45	Acetone/Pet. ether	$C_{21}H_{16}N_5O_3SCl$	55.56 (55.81)	3.53 (3.72)	15.44 (15.20)
5d	6-Br	o-OH	246	46	Acetone/Pet. ether	$C_{21}H_{15}N_5O_3SCl$	47.32 (47.01)	2.82 (2.51)	13.14 (13.36)
5e	H	p-OH	115	42	Ethanol/Water	$C_{23}H_{21}N_6O_2SCl$	55.56 (55.35)	3.53 (3.32)	15.44(15.60)
5f	6-Br	p-OH	240	44	Ethanol/Water	$C_{21}H_{15}N_5O_3SClBr$	47.32 (47.50)	2.82 (2.99)	13.14 (13.40)
5g	H	p-N$(CH_3)_2$	110	43	Methanol/Water	$C_{23}H_{21}N_6O_2SCl$	57.44 (57.23)	4.37 (4.60)	17.48 (13.36)
5h	6-Br	p-N$(CH_3)_2$	250	42	Methanol/Water	$C_{22}H_{18}N_5O_4S$	49.32 (49.47)	3.57 (3.20)	15.01 (14.92)
5i	H	m-OCH_3, p-OH	128	47	DMF	$C_{22}H_{18}N_5O_4SCl$	54.60 (54.78)	3.72 (3.95)	14.48 (14.23)
5j	6-Br	m-OCH_3, p-OH	238	45	DMF	$C_{22}H_{17}N_5O_4SClBr$	46.93 (46.78)	3.02 (2.86)	12.44 (12.75)
5k	H	o-OCH_3	150	44	Ethanol/Water	$C_{22}H_{18}N_5O_3SCl$	56.47 (56.26)	3.85 (3.98)	14.97 (14.72)
5l	6-Br	o-OCH_3	210	48	Ethanol/Water	$C_{22}H_{17}N_5O_3SClBr$	48.30 (48.45)	3.11 (3.02)	12.81 (12.99)
5m	H	p-OCH_3	175	46	Acetic Acid	$C_{22}H_{18}N_5O_3SCl$	56.47 (56.74)	3.85 (3.68)	14.97(14.80)

5n	6-Br	p-OCH_3	220	43	Acetic Acid	$C_{22}H_{17}N_5O_3SClBr$	48.30 (48.54)	3.11 (3.37)	12.81 (12.54)
6a	H	H	102	47	Ethanol/water	$C_{21}H_{17}N_5O_2S_2$	57.23 (57.70)	3.90 (3.71)	16.09 (16.20)
6b	6-Br	H	230	48	Ethanol/water	$C_{21}H_{16}N_5O_2S_2Br$	49.02 (49.15)	3.11 (3.96)	13.60 (13.39)
6c	H	o-OH	110	46	Methanol/water	$C_{21}H_{19}N_5O_3S_2$	55.57 (60.00)	3.76 (4.21)	16.71(16.52)
6d	6-Br	o-OH	265	48	Methanol/water	$C_{21}H_{16}N_5O_3S_2Br$	47.54 (47.78)	3.01 (3.31)	13.20 (13.15)
6e	H	p-OH	125	45	DMF	$C_{21}H_{17}N_5O_3S_2$	61.14 (60.32)	4.05 (4.36)	16.71(16.57)
6f	6-Br	p-OH	270	47	DMF	$C_{21}H_{16}N_5O_3S_2Br$	50.60 (50.85)	3.21 (3.09)	16.06 (14.29)
6g	H	p-$N(CH_3)_2$	420	45	Acetic Acid	$C_{21}H_{22}N_6O_2S_2$	57.74 (57.90)	4.60 (4.38)	17.57 (17.78)
6h	6-Br	p-$N(CH_3)_2$	260	44	Acetic Acid	$C_{23}H_{21}N_6O_2S_2Br$	49.55 (49.79)	3.77 (4.00)	15.08 (15.20)
6i	H	m-OCH_3, p-OH	135	48	Methanol/Water	$C_{22}H_{19}N_5O_4S_2Br$	54.88 (54.68)	3.95 (3.80)	14.55 (14.79)
6j	6-Br	m-OCH_3, p-OH	234	46	Methanol/Water	$C_{22}H_{18}N_5O_4S_2Br$	47.14 (47.30)	3.21 (3.32)	12.50 (12.35)
6k	H	o-OCH_3	140	45	DMF	$C_{22}H_{19}N_5O_3S_2$	55.77 (55.58)	4.20 (4.09)	15.48 (15.70)
6l	6-Br	o-OCH_3	280	43	DMF	$C_{22}H_{18}N_5O_3S_2Br$	47.36 (47.56)	3.30 (3.19)	13.15 (13.00)
6m	H	p-OCH_3	155	44	Ethanol/Water	$C_{22}H_{19}N_5O_3S_2$	56.77 (55.90)	4.20 (4.49)	15.48 (15.25)
6n	6-Br	p-OCH_3	295	45	Ethanol/Water	$C_{22}H_{18}N_5O_3S_2Br$	48.52 (48.70)	3.30 (3.15)	12.88 (15.10)

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