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Synthesis of 3-substituted quinazolinones as antifungal agents

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ABSTRACT

2-methyl-(3-sydnon-(3′-yl))monosubstitutedquinazolin-4(3H)-one, 2-methyl-3 –(sydnon-(4'-bromo-3'-yl))-monosubstitutedquinazolin-4(3H)-one,2-methyl-3-(sydnon-4-substitutedniline -3′-yl)mono substituted quinazolin-4 (3H) one 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. © 2011 Trade Science Inc. - INDIA

KEYWORDS

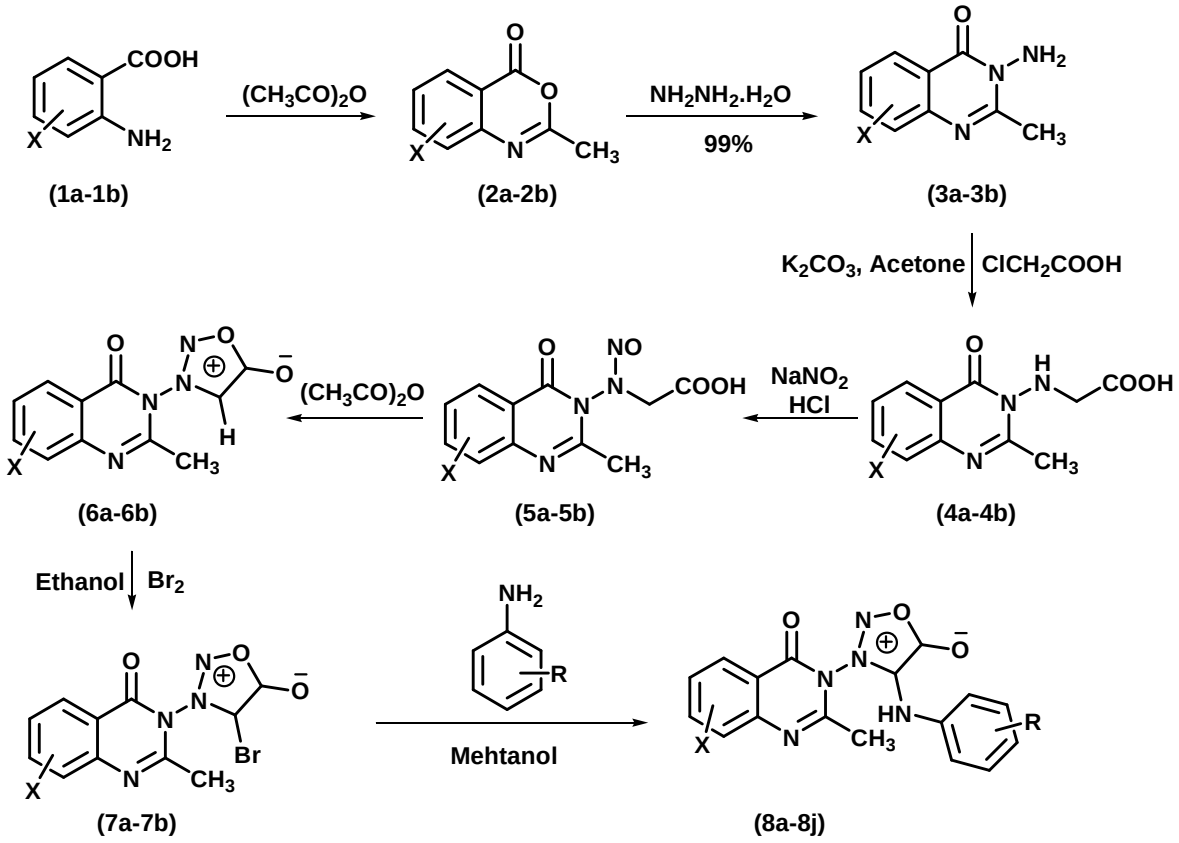
Quinazolinone;
Sydnone;
Anti-fungal activity.

INTRODUCTION

Among a wide variety of heterocycles that have been explored for developing pharmaceutically important molecules of Quinazolenone, have played an important role in medicinal chemistry. Qunizolenones have been shown a wide variety of biological and pharmacological activities like anticonvulant[1], anti-inflammatory[2,3] and antibacterial[4,5]. Some of them have been received considerable attention as potential antifungal[6-10] agents. Substitution pattern in quinazolenone nuclei suggest that substitution at 2 & 3 positions markedly modulate antifungal activity. Several workers have also synthesized 2,3-substituted quinazolenone containing different hetero systems which were found to posses potent anti fungal activities. Various derivatives of quinazolinone have been synthesized and evaluated for their antifungal activity.

RESULTS

2-amino-5-bromobenzoic acid **(1b)** was prepared from anthranilic acid and bromine. The reaction of compound **(1b)** with acetic anhydride furnished 2-methyl-6-bromo-4H-3,1-benzooxazin-4-one **(2b)**, Compound **(2b)** when further treated with hydrazine hydrate yielded3-anilino-2-methyl-6-bromoquinazolin-4(3H)-one **(3b)**. On acetylation by chloroacetic acid compound **(3b)** was converted into 2-[2′-methyl-6-bromoquinazolin-4′-(3H)-on-3′yl]amino acetic acid **(4b)**. Compound **(4a)** & **(4b)** can nitrosation in presence of HCl gives 2-N-nitroso-N-[2′-methyl-6′-bromoquinazolin-4′-(3H)-on-3′-yl] imino aceticacid **(5b)** & **(5b)**. Compound **(5b)** was cyclised into 2-methyl-(3-sydnon-(3′-yl))-6-bromoquinazolin-4-(3H)-one **(6b)** on reaction with acetic anhydride, which on reaction with ethanol/ bromine compound **(6a)** & **(6b)** afforded compounds **(7a)** and **(7b)**. Compounds **(7a)** and **(7b)** are converted into their corresponding substituted anlino congeners i.e. 2-methyl-3-sydnon-[4′-substitutedanilino-3′-yl)mono substituted quinazolin-4-(3H)-ones **(8a-8j)** on reaction with different aromatic amines. The structure of all by compounds was confirmed by their analytical (C, H, N) and spectral (IR, ^{1}H NMR) data. The All the



Scheme 1

compounds have been screened for their anti-fungal activity.

Compounds **(6a)**, **(6b)**, **(7a)**, **(7b)** & **(8a-8j)**, and the reference drugs fluconazole and griseofulvin were evaluated for antifungal activity at a concentration of 100mg/It against different strains of fungi. Compounds **(8d)** and **(8h)** were found to be the most potent compounds of the present series. Compound **(8d)** was found to possess more potent antifungal activity in comparision to the standards against C.albicans, C.albicans ATCC, C.parapsilosis 22019, A. fumigatus and A. niger and showed eqipotency towards C.krusei. On the other hand compound **(8h)** was more active against C.albicans, C.glabrata H05, C.parapsilosis 22019, and A.niger and equipotent towards C.albicans ATCC, and A.fumigatus. Compounds **(8f)** and **(8j)** also revealed satisfactorily good antifungal activity, though it was not better as compared to the standards but was found to be equipotent to fluconazole and griseofulvin (reference drugs). All the other compound of the series were found to be active against one or the other fungal strains used and displayed mild to moderate as well as optimal activity. The results for the antifungal activity of the compounds of this series are depicted in TABLE 1 for Candida and Aspergillus species.

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[11] 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

TABLE 1 : Pharmacological data of compounds (6a), (6b), (7a-7b) and (8a-8j)

Compounds	Antifungal activity # [diameter of inhibition zone (mm)]					Antifungal activity # [diameter of inhibition zone (mm)]		
	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
6a	-	8	-	4	-	-	10	-
6b	13	12	-	8	6	-	26	-
7a	-	-	6	-	7	-	15	-
7b	17	16	-	10	9	-	30	-
8a	-	-	9	-	9	-	15	-
8b	20	18	10	-	12	-	55	-
8c	12	10	-	11	-	-	50	-
8d	35	30	18	11	25	86	94	-
8e	14	18	12	-	-	-	46	-
8f	22	24	20	16	-	78	78	-
8g	18	17	-	-	15	-	82	50
8h	34	26	-	22	26	70	96	83
8i	20	-	11	-	-	-	80	38
8j	27	21	14	16	20	-	88	66

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

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 resultant solution was 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 were 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)×100 / C

where, 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.

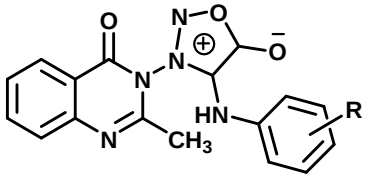
Standard agar disc diffusion method[12]

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.

EXPERIMENTAL

The melting points of the compounds were deter-

TABLE 2 : Physical and analytical data of 2-methyl-3-(4′-substituted anilinosydnon-3′-yl)monosubstitutedquinazolin-4(3H)-one (8a-8j)



Compd. No.	X	R	M.P. (°C)	Yield (%)	Recrystallisation solvent	Molecular formula	Elemental analysis (%) Calculated/Found		
							C	H	N
8a.	H	H	150	60	Methanol	$C_{17}H_{13}N_5O_2$	63.95/63.79	4.07/3.87	10.03/10.20
8b.	6-Br	H	260	61	Methanol	$C_{17}H_{12}N_5O_2Br$	51.25/51.00	3.02/3.26	17.58/17.30
8c.	H	o-OCH_3	125	62	Methanol	$C_{18}H_{15}N_5O_2$	64.86/64.97	4.50/4.25	21.02/21.30
8d.	6-Br	o-OCH_3	260	60	Methanol	$C_{18}H_{14}N_5O_2Br$	52.43/52.20	3.39/3.16	16.99/16.72
8e.	H	p-OCH_3	130	56	Methanol	$C_{18}H_{15}N_5O_2$	64.86/64.97	4.52/4.25	11.51/11.32
8f.	6-Br	p-OCH_3	280	59	Methanol	$C_{18}H_{14}N_5O_2Br$	52.43/52.20	3.39/3.16	16.99/16.77
8g.	H	o-Cl	140	58	Methanol	$C_{17}H_{12}N_5O_2Cl$	59.47/59.25	3.49/3.30	2.04/2.25
8h.	6-Br	o-Cl	280	60	Methanol	$C_{17}H_{11}N_5O_2Cl$	47.22/47.09	2.55/2.78	1.62/1.42
8i.	H	p-Cl	148	60	Methanol	$C_{17}H_{12}N_5O_2Cl$	59.47/59.25	3.49/3.30	2.04/2.25
8j.	Br	p-Cl	288	62	Methanol	$C_{17}H_{11}N_5O_2ClBr$	47.22/47.09	2.55/2.78	1.62/1.42

mined 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.

5-bromoanthranilic acid (1b)

This was prepared according to the method of Wheeler and Oats[13]. Bromine (0.8 mol) in acetic acid (20 ml) was added dropwise to the solution of anthranillic acid (0.4 mol) in absolute acetic anhydride (50 ml. The solid was separated to give 5-bromoanthranilic acid. The solid this crystallized out was washed with water and dried.

M.P. 209ºC; Yield 61%; Recrystallisation solvent methanol, molecular formula: $C_7H_6O_2NBr$. Wheelar and Oats[13] reported M.P. 210ºC; Yield 60%.

Acetanthranils or benzoxinones (2)

These were prepared according to the method given by Bogert and Soil[14]. An appropriate mixture of anthranilic acid (0.01 mol) and acetic anhydride (0.02 mol) was refluxed for 2-3 hours with occasional stirring. The excess of acetic anhydride was distilled off. On cooling, a solid separated out, which was filtered, washed with petroleum ether (40º-60ºC) and dried in vacuo. The acetanthranils thus separated are given below:

Acetanthranil (2a)

M.P. 78ºC; Yield; 60%; Recrystallisation solvent petroleum ether. IR (KBr) (cm^{-1}): 1520 (C····C of aromatic), 1620 (C=N), 1720 (C=O), 3060 (aromatic C-H). ^1H-NMR ($CDCl_3$+DMSO-d_6) δ (ppm): 1.80 (s, 3H, CH_3), 7.25-7.65 (m, 4H, Ar-H), Molecular formula $C_9H_7NO_2$, Elemental analysis: Calcd. C 67.08, H 4.34, N 8.69; Found. C 67.29, H 4.58, N 8.81.

6-bromoacetanthranil (2b)

M.P. 174º; Yield 65%; Recrystallisation solvent pe-

troleum ether; IR (KBr) (cm^{-1}): 630 (C-Br), 1549 (C····C of aromatic), 1620 (C=N), 1720 (C=O), 3060 (aromatic C-H). ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ (ppm): 1.60 (s, 3H, CH_3), 7.20-7.50 (m, 3H, Ar-H). Molecular formula $C_9H_6NO_2Br$, Elemental analysis: Cacld.: C 45.00, H 2.50, N 5.83; Found: C 45.31; H 2.31; N 5.96.

3-amino-2-methylmonosubstituted-quinazolin-4(3H)-ones (3)

An appropriate amount of acetanthranils (0.01 mol) and hydrazine hydrate (99%, 0.02 mol) were mixed together in methanol (dry, 50 ml) and the resulting mixture was refluxed for 8 hours. The excess of methanol was distilled off in vacuo. The residue on cooling gave a crystalline solid. The products thus obtained are given below:

3-amino-2-methylquinazolin-4(3H)-one (3a)

M.P. 156ºC; Yield 65%; Recrystallaisation solvent ethanol. IR (KBr) (cm^{-1}): 1545 (N-N), 1540 (C····C of aromatic), 1625 (C=N), 1660 (C=O), 3044 (aromatic C-H), 3260 (NH_2). ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ (ppm): 2.15 (s, 3H, CH_3), 7.80 (bs, 2H, NH_2, exchangeable with D_2O), 7.22-7.72 (m, 4H, Ar-H). Molecular formula $C_9H_9N_3O$; Elemental analysis; Cacld.: C 61.71, H 24.00, N 5.14; Found: C 61.76, H 24.24, N 5.43; MS: $[M]^+$ m/z 175.

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

M.P. 196ºC; Yield 65; Recrystallisation solvent ethanol; IR (KBr) (cm^{-1}): 602 (C-Br), 1540 (N-N), 1554 (C····C of aromatic), 1610 (C=N), 1680 (C=O), 3040 (aromatic C-H), 3260 (NH_2). ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ (ppm): 2.20 (s, 3H, CH_3), 7.56 (bs, 2H, NH_2, exchangeable with D_2O), 7.32-8.20 (m, 3H, Ar-H). Molecular formula $C_9H_8N_3OBr$; Elemental analysis; Cacld.: C 42.51, H 3.14, N 16.53; Found: C 42.31; H 3.26, N 16.63. MS: $[M]^+$ m/z 254.

2-(2′-methyl mono substituted quinazolin-4′-(3H) on-3′-yl) amino acetic acid (4)

To a solution of 3-amino-2-methyl mono substituted quinazolinone (0.01 mole) in acetone (dry, 80ml), chloro acetic acid (0.01 mole) and anhydrous K_2CO_3 (50g) were added. The reaction mixture was refluxing; excess of solvent was distilled off. The solid thus separated out is washed with water.

2-(2′-methylquonazolin-4′(3H)-on-3′-yl) amino acetic acid (4a)

M.P. 90°C; Yield 72%; Recrystallisation solvent methanol/water; IR (KBr) (cm^{-1}) : 152 (N-N), 1548 (C=C of aromatic), 1594 (C=N), 1682 (C=O), 1712 (COOH), 2840 (CH_2), 2915 (CH_3), 3053 (aromatic CH), 3342 (N-H). ^{1}H NMR ($CDCl_3$ + $DMSOd_6$) δ (ppm): 2.32 (s, 3H, CH_3), 4.63 (d, 2H, CH_2), 6.84 (ss, 1H, NH), 7.40-8.15 (m, 4H, Ar-H), 9.56 (s, 1H, COOH), Molecular formula: $C_{11}H_{11}N_3O_3$; Elemental analysis: Cacld.: C 56.65, H 4.72, N 18.00; Found: C 56.50; H 4.86; N 18.16. MS: $[M]^+$ m/z 233.

2-(2′-methyl-6′-bromoquinazolin-4′(3H)on-3′-yl) amino acetic acid (4b)

M.P. 160° yield 75%, IR(KBr) (cm^{-1}): 600 (C-Br), 1520 (N-N), 1550 (C=C of aromatic), 1590 (C=N), 1685 (C=O), 1715 (COOH), 2845 (CH_2), 2918 (CH_3), 3050 (aromatic CH), 3340 (N-H). ^{1}H NMR ($CDCl_3$+$DMSOd_6$) δ (ppm): 2.35 (s, 3H, CH_3), 4.60 (d, 2H, CH_2), 6.80 (ss, 1H, $NHCH_2$), 7.45-8.10 (m 3H Ar-H)) 9.54 (s, 1H, COOH). Recrystallisation solvent methanol/water, Molecular formula: $C_{11}H_{10}N_3O_3Br$; Elemental analysis: Cacld.: C 42.31, H 3.20, N 13.58; Found: C 42.45, H 3.12, N 13.46. MS: $[M]^+$ m/z 312.

2-N-nitroso-N-(2′-methyl-6′-mono substituted quinazolin-4′(3H)-on-3′-yl) imino acetic acid (5)

To a well stirred solution of 2-(2′-methyl-6′-mono-substituted quinazolin-4′-(3H)-on-3′-yl) amino acetic acid **(4)** (0.01 mole) in 40% hydrochloric acid (100ml) at 0-5°C, a solution of sodium nitrite (0.01 mole) in water (25ml), was added drop wise during 30 min. The reaction mixture was allowed to stand over right filtered, washed thoroughly with ice cold water and dried in air.

2-N-nitroso-N-(2′-methyl quinazolin-4′-(3H)-on-3′-yl) imino acetic acid (5a)

M.P. 82°C, yield 69%, Recrystallisation solvent methanol/water; IR (KBr) (cm^{-1}): 1533 (N-N), 1580 (C=C of aromatic), 1603 (C=N), 1665 (C=O), 1702 (COOH, 2841 (CH_2), 2915 (CH_3), 3058 (aromatic

C-H), ^{1}H NMR ($CDCl_3$ + $DMSOd_6$) δ (ppm): 2.45 (s, 3H, CH_3), 4.42 (ss, 2H, CH_2), 7.50-7.95 (m, 4H, Ar-H), 9.52 (s, 1H, COOH), Molecular formula: $C_{11}H_{10}N_4O_4$; Elemental analysis: Cacld.: C 50.38, H 3.82, Found: C 50.52; H 3.65, N 21.37; Found 21.29. MS: $[M]^+$m/z 262.

2-N-nitroso-N-(2′-methyl-6′-bromoquinazolin-4′-(3H)-on-3′-yl) iminoacetic acid (5b)

M.P. 196°C yield 72%, Recrystallisation solvent methanol/water; IR (KBr) (cm^{-1}) : 605 (C-Br), 1530 (N-N), 1582 (C=C of aromatic), 1600 (C=N), 1668 (C=O), 1700 (COOH), 2848 (CH_2), 2918 (CH_3) 3060 (aromatic), ^{1}H NMR ($CDCl_3$ + $DMSOd_6$) δ (ppm) : 2.48 (s, 3H, CH_3), 4.40 (ss, 2H, CH_2), 7.25-7.80 (m, 3H, Ar-H), 9.50 (s, 1H, COOH), Molecular formula: $C_{11}H_9N_4O_4Br$; Elemental analysis: Cacld.: C 38.71, H 2.6, N 16.42; Found: C 38.82, H 2.50, N 16.55. MS: $[M]^+$ m/z 341.

2-methyl-(3-sydnon-(3′-yl))monosubstituted quinazolin-4(3H)-one (6)

Compound **(5a)** & **(5b)**, was heated with acetic anhydride (1:5 by weight) on a water bath for 2-4 hours and then poured into crushed ice to furnish 2-methyl-(3-sydnon-(3′-yl)) monosubstituted quinazolin-4(3H)-one.

2-methyl-3-sydnon-(3′-yl)quinazolin-4-(3H)-one (6a)

M.P.97°C, yield 74%, Recrystallisation solvent benzene; IR (KBr) (cm^{-1}): 842 (N-O), 1097 (C-O), 1535 (N-N), 1580 (C=C of aromatic), 1605 (C=N), 1664)C=O), 1755 (C=O of sydnone), 2912 (CH_3), 3055 (aromatic CH). ^{1}H NMR ($CDCl_3$ + $DMSOd_6$) δ (ppm) : 2.52 (s, 3H, CH_3), 6.50 (s, 1H, sydnone C-H), 7.30-8.15 (m, 4H, Ar-H). Molecular formula: $C_{11}H_8N_4O_3$; Elemental analysis: Cacld.: C 54.09, H 3.28, N 22.95; Found: C 54.24, H 3.47, N 22.65. MS: $[M]^+$ m/z 244.

2-methyl-(3-sydnon-(3′-yl))-6-bromo quinazolin-4(3H)-one (6b)

M.P. 195° C, yield 70%, Recrystallisation solvent benzene; IR (KBr) (cm^{-1}): 600 (C-Br), 840 (N-O), 1995 (C-O), 1530 (N-N), 1584 (C=C of aromatic), 1600 (C=N), 1660 (C=O), 1750 (Sydnone C=O), 2910 (CH_3), 3058 (aromatic C-H). ^{1}H NMR ($CDCl_3$ + $DMSOd_6$) δ (ppm): 2.50 (s, 3H, CH_3), 6.8 (s, 1H, sydnone C-H), 7.35-8.10 (m, 3H, Ar-H), Molecular formula: $C_{11}H_7N_4O_3Br$; Elemental analysis; Cacld.: C 40.87, H 2.17, N 17.34; Found: C 40.67, H 2.24, N 17.26. MS: $[M]^+$ m/z 323.

2-methyl-3(sydnon-(4′-bromo-3′-yl))-monosubstituted quinazolin-4(3H)-one (7)

To a suspension of 2-methyl-3-(sydnon(3′-yl)] monosubstituted quinazolin-4(3H)-one **(6)** (0.005 mole/ 1.0g) in ethanol (40 ml), sodium bicarbonate (2.0g/ 0.0024 mole) was added at room temperature. The cloudly solution thus obtained became clear on addition of bromine (0.9 g/0.5 mole) in ethanol (25ml). The reaction mixture thus obtained was stirred further for 30 min and diluted with water (200 ml) and then filtered. The solid thus separated out was recrystallised to give compound **(7)**.

2-methyl-3(sydnon-(4′-bromo-3′-yl))quinazolin-4(3H)-one (7a)

M.P.105°C, yield 65%, Recrystallisation solvent ethanol; IR (KBr) (cm^{-1}): 615 (C-Br), 840 (N-O), 1090 (C-O), 1530 (N-N), 1570 (C⋯C of aromatic), 1610 (C=N), 1650 (C=O), 1750 (C=O of sydnone), 2920 (CH_3), 3050 (aromatic CH). ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ (ppm): 2.20 (s, 3H, CH_3), 7.15-8.45 (m, 4H, Ar-H). Molecular formula: $C_{11}H_7N_4O_3Br$; Elemental analysis: Cacld.: C 40.86, H 20.17, N 14.86; Found: C 40.62, H 2.32, N 14.71. MS: $[M]^+$ m/z 323.

2-methyl-3(sydnon-(4′-bromo-3′-yl)]-6-bromo-quinazolin-84(3H)-one (7b)

M.P. 225°C, yield 67%, Recrystallisation solvent ethanol; IR (KBr) (cm^{-1}): 610 (C-Br), 840 (N-O), 1090 (C-O), 1530 (N-N), 1578 (C=C of aromatic), 1615 (C=N), 1650 (C=O), 1760 (sydnone C=O), 2905 (CH_3), 3050 aromatic C-H). ^{1}H NMR ($CDCl_3$ + $DMSOd_6$) δ (ppm): 2.48 (s, 3H, CH_3), 6.48 (s, 1H, sydnone C-H), 7.25-7.80 m, 3H, Ar-H). Molecular formula: $C_{11}H_6N_4O_3Br_2$; Elemental analysis: Cacld.: C 40.86, H 2.17, N 14.86; Found: C 40.62, H 2.32, N 14.71. MS: $[M]^+$ m/z 402.

2-methyl-3(sydnon-4-substitutedanilino-3-yl) monosubstitutedquinazolin-4-(3H)-one (8)

A solution of 2-methyl-3-(sydnon-(4′-bromo-3′-

yl)) mono substituted quinazolin-4(3H)-one **(7)** (0.02 mole) in methanol (80 ml) was refluxed with substituted andine derivative (0.02 mole) for 6-ons excess of solvent was distilled off, cooled, poured into crushed ice and filtered. The solid thus separated was washed with petroleum ether (40-60°C).

2-methyl-3(sydnon-4′-(o-methoxy) anilino-3′-yl)-quinazolin-4(3H)-one (8c)

M.P. 125°C, yield 62%, Recrystallisation solvent methanol; IR (KBr) (cm^{-1}): 845 (N-O), 1095 (C-O), 1540 (N-N), 1585 (C=C of aromatic), 1619 (C=N), 1660 (C=O), 1769 (sydnone C=O), 2910 (CH_3), 3060 (aromatic CH). ^1H NMR ($CDCl_3$ + $DMSOd_6$) δ (ppm): 2.50 (s, 3H, CH_3), 3.42 (s, 3H, Ar-OCH_3) 5.52 (brs, 1H, N<u>H</u>-Ar) 6.45 (s, 1H, sydnone CH), 7.30-7.80 (m, 8H, Ar-H). Molecular formula: $C_{18}H_{15}N_5O_4$; Elemental analysis: Cacld.: C 64.86, H 4.50, N 31.02; Found: C 64.97, H 4.25, N 21.32. MS: $[M]^+$ m/z 365.

2-methyl-3(sydnon-4′-(o-methoxy)-amino-3′-yl)-6-bromo quinazolin-4(3H)-one (8d)

M.P. 260°C, yield 60%, Recrystallisation solvent methanol; IR (KBr) (cm^{-1}): 600 (C-Br), 845 (N-O), 1091 (C-O), 1510 (C-N), 1535 (N-N), 1580 (C=C of aromatic 1611 (C=N), 1654 (C=O), 1764 (sydnone C=O), 2903 (CH_3), 3055 (aromatic CH). ^1H NMR ($CDCl_3$ + $DMSOd_6$) δ (ppm): 3.40 (s, 3H, Ar-OCH_3) 5.54 (brs, 1H, N<u>H</u>-Ar), 6.48 (s, 1H, sydnone C-H), 7.20-7.95 (m, 7H, Ar-H). Molecular formula: $C_{18}H_{14}N_5O_4Br$; Elemental analysis: Cacld.: C 52.43, H 3.39, N 16.99; Found: C 52.20, H 3.16, N 16.72. MS: $[M]^+$ m/z 444.

Other derivatives were prepared following the same method as described above. Their physical and analytical data are given in TABLE 2.

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