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Synthesis and Antihyperglycemic Activity of Suitably Functionalized 3H-quinazolin-4-ones†

Vishnu Ji Ram,[a,*] Farhanullah,[a] Brajendra K. Tripathi[b] and Arvind K. Srivastava[b]

[a]*Division of Medicinal Chemistry, Central Drug Research Institute, Lucknow 226001, India*
[b]*Division of Biochemistry, Central Drug Research Institute, Lucknow 226001, India*

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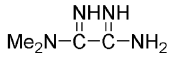
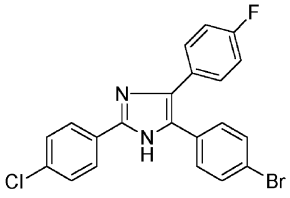
Abstract—A series of 2-*sec*-amino-3H-quinazolin-4-ones (**4a**–**p**) and 4-*sec*-amino-2-chloroquinazolines (**5a**–**b**) have been synthesized by nucleophilic substitution reaction of 2-chloro-4(3H)-quinazolones (**3**) and 2,4-dichloroquinazolines (**2**) with amines, respectively. Most of the synthesized compounds were evaluated for antihyperglycemic activity but only **4a**,**b**,**d**,**j**,**o** displayed significant reduction in blood glucose level in streptozotocin and sucrose loaded rat models.

Introduction

Diabetes mellitus is a group of metabolic disorders with different etiologies, characterized by hyperglycemia due to underutilization of glucose. Non-insulin-dependent diabetes mellitus (NIDDM) is very common, results either from insulin resistance, inadequate secretion of insulin or hepatic glucose production. Metformin (**I**), an antihyperglycemic drug, acts as an inhibitor of hepatic glucose production, possesses guanidine and amidine functionalities in its molecular structure. Another class of compound, triarylimidazoles (**II**), which has also amidine moiety in a cyclic structure, displays significant glucagons antagonistic property. Whether the presence of an amidine or guanidine moiety in a linear chain is essential for antihyperglycemic activity, bicyclic compounds with amidine and guanidine pharmacophores in a cyclic form were designed to explore their blood sugar lowering property.



I



II

Quinazolines, a cyclic amidine are known for diverse pharmacological activities as anticonvulsant,[1,2] sedative, antihypertensive,[3] vasodilator,[4] phosphodiesterase inhibitors[5] and fibrinogen receptor antagonists[6] but their hypoglycemic activity has not been studied extensively.[7]

Chemistry

2-*sec*-Amino-3H-quinazolin-4-ones have previously been prepared[8] from the reaction of anthranilic acid and potassium thiocyanate followed by *S*-methylation of 2-thio-4-oxo-tetrahydroquinazoline and nucleophilic substitution by secondary amines. The disadvantage associated with this procedure is the presence of trace quantities of methyl mercaptan even after crystallization which causes nausea. Thus, an alternative procedure not involving liberation of methyl mercaptan was needed. A second approach (Scheme 1) is based on the synthesis of quinazolin-2,4-diones,[9] obtained through fusion of anthranilic acid with urea at 140 °C. The dione (**1**) thus formed was halogenated with $POCl_3$ to yield 2,4-dichloroquinazoline (**2**) which was regioselectively hydrolyzed to 2-chloro-3H-quinazolin-4-ones (**3**) in 2% aqueous sodium hydroxide.[9] Reaction of **3** and secondary amines provided 2-*sec*-amino-3H-quinazolin-4-ones (**4**). The chloro group at position 4 in 2,4-dichloroquinazolines is more reactive[10] compared to 2-chloro and thus the former underwent nucleophilic substitution reaction with amines to yield 4-*sec*-amino-2-chloroquinazolines (**5**).

*Corresponding author. Tel.: +91-522-212416; fax: +91-522-223405; e-mail: vjiram@yahoo.com
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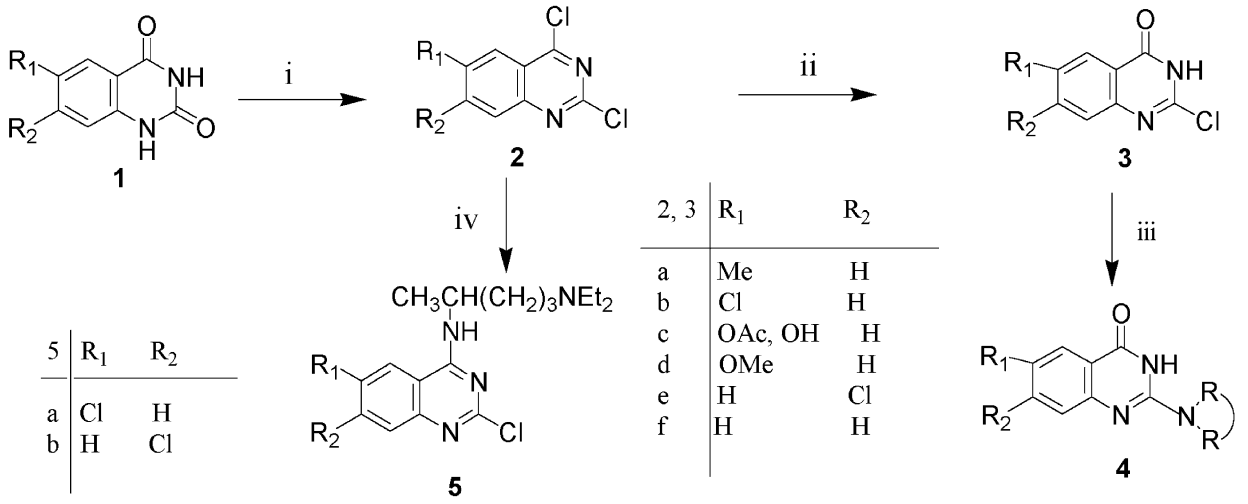


Scheme 1. Reagent and conditions: (i) $POCl_3$/*N*,*N*-dimethylaniline/115 °C; (ii) 2% aq NaOH/30 °C; (iii) $HN(R)_2/C_2H_5OH$/85 °C; (iv) *N*′,*N*′-diethylpentan-1,4-diamine/C_2H_5OH/85 °C.

Results and Discussion

Most of the synthesized compounds were evaluated for in vivo antihyperglycemic activity in male Sprague–Dawley rats of body weight (160 ± 20 g) in two different models.

Streptozotocin (STZ) model

A solution of streptozotocin (60 mg/kg) in 100 mM citrate buffer, pH 4.5 was prepared and calculated amount of the fresh solution was dosed to overnight fasted rats (60 mg/kg) intraperitoneally. The blood sugar level was measured after 48 h by glucometer. Animals showing 200–400 mg/dl were selected for antidiabetic screening. The diabetic animals were divided into groups of six animals each. Rats of experimental group were administered a suspension of the desired test sample (prepared in 1% gum acacia) orally (100 mg/kg body weight). Controlled group animals were also fed with 1% gum acacia. The blood glucose levels were measured at 1-, 2-, 3-, 4-, 5-, 6-, 7- and 24-h intervals. The % fall in blood glucose from 1 to 24 h by test sample was calculated according to the area under curve (AUC) method. The average fall in AUC in experimental group compared to control group provided% antihyperglycemic activity.

Sucrose-loaded (SLM) model

Overnight fasted male Sprague–Dawley rats were used for sucrose-loaded experiment. Blood was collected initially and thereafter test compounds were given to the test group consisting of five rats by oral gavage at a dose of 100 mg/kg body weight. After half an hour post-test treatment, a sucrose load of 10 gm/kg body weight was given to each rat. Blood was collected at 30, 60, 90 and 120 min post sucrose load. The% fall in blood glucose level was calculated according to the AUC method.

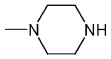
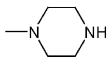
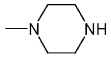
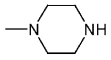
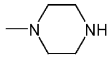
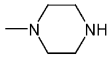
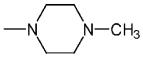
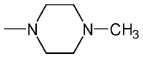
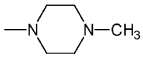
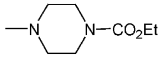
Among the 16 screened compounds only **4a**,**b**,**d**,**j**,**o** demonstrated antihyperglycemic activity in STZ model while two additional compounds **4e** and **4p**, displayed blood glucose lowering activity at 100 mg/kg dose in SLM model.

Of these five active compounds, 2-piperazinylquinazolin-4(3H)-one hydrochloride (**4a**) reduced blood glucose level to 58 and 77% in STZ and SLM models, respectively. The other active compound 2-(*N*-ethoxycarbonylpieprazinyl)-quinazolin-4(3H)-one (**4j**) also displayed moderate antihyperglycemic activity (21.5%), possibly due to its slow transformation to the highly active metabolite 2-piperazinylquinazolin-4(3H)-one (**4a**) but was found inactive in SLM model. A Compound with chloro substituent at position 7 and pyrrolidine group at position 2 (**4o**) displayed a significant blood glucose lowering activity (52.9%) in SLM model while only 12.4% reduction in blood glucose level in STZ model. A compound with piperidinyl substituent at position 2 displayed low order of activity (9.2%) in SLM model. It is evident from Table 1 that, the presence of chloro substituent at position 6 in quinazoline ring (**4c**,**h**,**n**) caused a complete loss of antihyperglycemic activity. Two compounds, 6-methyl-2-piperazinylquinazolin-4(3H)-one (**4b**) and 6-hydroxy-2-piperazinylquinazolin-4(3H)-one (**4d**), reduced blood glucose level by 14.8 and 13.4%, respectively, in STZ model while latter demonstrated significant activity (38%) in SLM model. Presence of piperidinyl or pyrrolidinyl substituent at position 2 results in a complete loss or reduction in antihyperglycemic activity, with exception of 7-chloro-2-pyrrolidinylquinazolin-4(3H)-one (**4o**) which reduced the blood glucose level by 12.4% in STZ model. Metformin and glybenclamide were used as standard antidiabetic drug in both the models.

Experimental

Melting points were determined on Büchi-530 capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Bruker WM 200 MHz spec-

Table 1. In vivo antihyperglycemic activity of various quinazoline derivatives (**4a–p**) in streptozotocin (STZ) and sucrose-loaded (SLM) rat models

4		R_1	R_2	% Blood sugar lowering activity (100 mg/kg)	
				STZ model	SLM model
a		H	H	58.0	77.0
b		Me	H	14.8	33.0
c		Cl	H	NIL	NIL
d		OH	H	13.4	38.0
e		OMe	H	NIL	16.0
f		H	Cl	NIL	NIL
g		Me	H	NIL	NIL
h		Cl	H	NIL	NIL
i		OH	H	NIL	NIL
j		H	H	21.5	NIL
k		Me	H	NIL	NIL
l		OH	H	NIL	NIL
m		OAc	H	NIL	NIL
n		Cl	H	NIL	NIL
o		H	Cl	12.4	52.9
p		H	Cl	NIL	9.2
	Metformin			19.1	12.9
	Glybenclamide			29.0	33.7

NIL, insignificant blood sugar lowering activity.

trometer in deuterated solvents with TMS as internal reference. IR spectra of all compounds were recorded on Perkin–Elmer AC-1 spectrometer. Mass spectra of all compounds were measured with Jeol JMS-D 300 spectrometer (70 eV). Microanalyses were determined on Carlo Erba EA-1108 element analyzer within $\pm 0.5\%$ of the theoretical values. Thin-layer chromatography (TLC) was performed on 7×3 cm precoated silica gel plastic plates. For column chromatography, silica gel of 60–120 mesh from Acme Synthetic Chemicals, Bombay, India was used.

General procedure for the preparation of 2,4-dichloroquinazolines (2a–g)

A mixture of quinazolin-2,4-diones (**1**, 2.0 g) and phosphorous oxychloride ($POCl_3$, 6 mL) was refluxed in presence of *N*,*N*-dimethylaniline (0.6 mL) for 5 h. Reaction mixture was allowed to cool to room temperature and poured into ice cold water with stirring. Precipitate obtained was filtered, washed with distilled water and finally purified on silica gel column chromatography using hexane/ethyl acetate (40:1) as eluent.

6-Methyl-2,4-dichloroquinazoline (2a). This was prepared by halogenation of 6-methylquinazolin-2,4-dione in 77% yield; mp 138–140 °C (lit.[11] mp 140 °C]; MS (EI) *m*/*z* 212 (M^+, 85.9).

2,4,6-Trichloroquinazoline (2b). This was obtained by halogenation of 6-choroquinazolin-2,4-dione in 69% yield; mp 133 °C (lit.[12] mp 131 °C); MS (EI) *m*/*z* 234 (M^+, 100.0).

6-Acetoxy-2,4-dichloroquinazoline (2c). Yield 51%; mp >250 °C; MS (EI) *m*/*z* 256 (M^+, 6.1), 216 (55.8), 214 (81.0), 179 (32.6); IR (KBr) 1762 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$) δ 2.44 (s, 3H, CH_3), 7.78 (dd, $J=9.2$, 2.8 Hz, 1H, ArH), 8.05–8.23 (m, 2H, ArH), Anal. calcd for $C_{10}H_6Cl_2N_2O_2$: C, 46.72, H, 2.35, N, 10.90. Found: C, 46.54, H, 2.49, N, 10.77.

2,4-Dichloro-6-methoxyquinazoline (2d). This was prepared by halogenation of 6-methoxyquinazolin-2,4-dione in 76% yield; mp 174 °C (lit.[12] mp 171 °C); MS (EI) *m*/*z* 228 (M^+, 100.0).

2,4,7-Trichloroquinazoline (2e). This was prepared by halogenation of 7-chloroquinazolin-2,4-dione in 78% yield; mp 130 °C (lit.[12] Mp 127 °C); MS (EI) *m*/*z* 234 (M^+, 100.0).

2,4-Dichloroquinazoline (2f). This was obtained by halogenation of quinazolin-2,4-dione in 72% yield; mp 116–117 °C (lit.[9] mp 116–117 °C); MS (EI) *m*/*z* 199 (M^+, 78.0).

General procedure for the preparation of 2-chloro-3H-quinazolin-4-ones (3a–f)

A suspension of 2,4-dichloro-quinazolines (**2**, 1 mmol) was stirred in 2% aqueous sodium hydroxide solution (3 mL) for 3 h. Reaction mixture was diluted with water (6 mL) and filtered to remove unreacted 2,4-dichloroquinazoline. Filtrate was neutralized with dilute acetic acid, precipitate thus obtained was filtered and washed with water.

2-Chloro-6-methyl-3H-quinazolin-4-one (3a). Yield 95%; mp 220–221 °C; MS (EI) *m*/*z* 194 (M^+, 84.8), 160 (17.9), 159 (100.0), 131 (13.5); IR (KBr) 1676.0 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$) δ 2.50 (s, 3H, CH_3), 7.13 (s, 1H, ArH), 7.29–730 (m, 1H, ArH), 7.94–7.95 (m, 1H, ArH). Anal. calcd for $C_9H_7ClN_2O$: C, 55.54, H, 3.63, N, 14.39. Found: C, 55.66, H, 3.52, N, 14.55.

2,6-Dichloro-3H-quinazolin-4-one (3b). This was obtained by partial hydrolysis of 2,4,6-trichloroquinazoline (**2b**) in 86% yield; mp >250 °C (lit.[13] mp 222–225 °C); MS (EI) *m*/*z* 215 (M^+, 66.9).

2-Chloro-6-hydroxy-3H-quinazolin-4-one (3c). Yield 82%; mp >250 °C; MS (EI) *m*/*z* 196 (M^+, 49.0), 161 (100.0); IR (KBr) 1662.0 (CO), 3638 cm^{-1} (OH); ^1H NMR (200 MHz, $CDCl_3$) δ 7.34 (dd, $J=9.2$, 2.8 Hz, 1H, ArH), 7.45 (d, $J=2.8$ Hz, 1H, ArH), 7.56 (d, $J=9.2$ Hz, 1H, ArH), 10.34 (brs, 1H, OH). Anal. calcd for $C_8H_5ClN_2O_2$: C, 48.88, H, 2.56, N, 14.25. Found: C, 48.74, H, 2.64, N, 14.38.

2-Chloro-6-methoxy-3H-quinazolin-4-one (3d). This was prepared by partial hydrolysis of 2,4-dichloro-6-methoxyquinazoline (**2d**) in 87% yield; mp >250 °C (lit.[13] mp 232–235 °C); MS (EI) *m*/*z* 210 (M^+, 100.0).

2,7-Dichloro-3H-quinazolin-4-one (3e). This was obtained by partial hydrolysis of 2,4,7-trichloroquinazoline (**2e**) in 92% yield; mp >250 °C (lit.[13] mp 219–224 °C]; MS (EI) *m*/*z* 215 (M^+, 39.7).

2-Chloro-3H-quinazolin-4-one (3f). This was prepared by partial hydrolysis of 2,4-dichloroquinazoline (**2f**) in 88% yield; mp 220–221 °C (lit.[9] mp 218–220 °C); MS (EI) *m*/*z* 180 (M^+, 50.8).

General procedure for the preparation of 2-*sec*-amino-3H-quinazolin-4-ones (4a–p)

A mixture of 2-chloro-3H-quinazolin-4-ones (**3**, 2 mmol) and piperazine (2 mmol) was refluxed in alcohol (5 mL) for 5–6 h. Alcohol was stripped off, residue thus obtained was purified by silica gel column chromatography using $CHCl_3$/MeOH (9:1) as eluent.

2-Piperazin-1-yl-3H-quinazolin-4-one hydrochloride (4a). Yield 78%; mp >250 °C (lit..[2] mp 200.5–211 °C]; MS (EI) *m*/*z* 230 (M^+, 19.7), 188 (17.68), 174 (100), 162 (100); IR (KBr) 1678 cm^{-1} (CO); ^1H NMR (200 MHz, D_2O) δ 3.20 (t, $J=4.6$ Hz, 4H, NCH_2), 3.76 (t, $J=4.6$ Hz, 4H, NCH_2), 6.96 (d, $J=9.2$ Hz, 1H, ArH), 7.11–7.18 (m, 1H, ArH), 7.39–7.47 (m, 1H, ArH), 7.66 (d, $J=9.2$ Hz, 1H, ArH). Anal. calcd for $C_{12}H_{14}N_4O{\cdot}HCl$: C, 54.04, H, 5.67, N, 21.01. Found: C, 54.16, H, 5.82, N, 21.25.

6-Methyl-2-piperazin-1-yl-3H-quinazolin-4-one hydrochloride (4b). Yield 83%; mp 221 °C; MS (EI) *m*/*z* 244 (M^+, 17.4), 202 (14.0), 188 (58.1), 176 (100); IR (KBr) 1672 cm^{-1} (CO); ^1H NMR (200 MHz, DMSO-d_6) δ 2.30 (s, 3H, CH_3), 2.62 (t, $J=4.6$ Hz, 4H, NCH_2), 3.51 (t, $J=4.6$ Hz, 4H, NCH_2), 7.05 (d, $J=9.2$ Hz, 1H, ArH), 7.39 (d, $J=9.2$ Hz, 1H, ArH), 7.66–7.68 (m, 1H, ArH). Anal. calcd for $C_{13}H_{16}N_4O{\cdot}HCl$: C, 55.61, H, 6.10, N, 19.96. Found: C, 55.70, H, 6.22, N, 19.99.

6-Chloro-2-piperazin-1-yl-3H-quinazolin-4-one hydrochloride (4c). Yield 84%; mp >250 °C; MS (EI) *m*/*z* 264 (M^+, 21.5), 222 (22.2), 207 (60.5), 196 (100.0); IR (KBr) 1679 cm^{-1} (CO); ^1H NMR (200 MHz, DMSO-d_6) δ 2.58 (t, $J=4.6$ Hz, 4H, NCH_2), 3.69 (t, $J=4.6$ Hz, 4H, NCH_2), 7.28 (d, $J=9.2$ Hz, 1H, ArH), 7.46 (dd, $J=9.2$, 2.8 Hz, 1H, ArH), 7.95 (d, $J=2.8$ Hz, 1H, ArH). Anal. calcd for $C_{12}H_{13}ClN_4O{\cdot}HCl$: C, 47.86, H, 4.69, N, 18.60. Found: C, 47.98, H, 4.87, N, 18.74.

6-Hydroxy-2-piperazin-1-yl-3H-quinazolin-4-one hydrochloride (4d). Yield 71%; mp >250 °C; MS (EI) *m*/*z* 246 (M^+, 11.6), 205 (16.7), 191 (36.9), 178 (59.3); IR (KBr) 1670 (CO), 3640 cm^{-1} (OH); ^1H NMR (200 MHz, DMSO-d_6) δ 2.57 (t, $J=4.6$ Hz, 4H, NCH_2), 3.59 (t, $J=4.6$ Hz, 4H, NCH_2), 7.07–7.12 (m, 1H, ArH), 7.19–7.25 (m, 2H, ArH), 9.62 (brs, 1H, NH), 9.70 (brs, 1H, OH). Anal. calcd for

$C_{12}H_{14}N_4O_2$·HCl: C, 50.98, H, 5.35, N, 19.82. Found: C, 50.76, H, 5.55, N, 19.94.

6-Methoxy-2-piperazin-1-yl-3H-quinazolin-4-one hydrochloride (4e). Yield 75%; mp >250 °C; MS (EI) *m/z* 260 (M^+, 41.4), 230 (14.4), 218 (25.5), 205 (26.9), 204 (100.0); IR (KBr) 1671 cm^{-1} (CO); ^1H NMR (200 MHz, DMSO-d_6) δ 2.60 (t, J = 4.6 Hz, 4H, NCH_2), 3.66 (t, J = 4.6 Hz, H, NCH_2), 3.92 (s, 3H, OCH_3), 7.10–7.12 (m, 2H, ArH), 7.17–7.20 (m, 1H, ArH), Anal. calcd for $C_{13}H_{16}N_4O_2$·HCl: C, 52.62, H, 5.77, N, 18.88. Found: C, 52.77, H, 5.89, N, 19.13.

7-Chloro-2-piperazin-1-yl-3H-quinazolin-4-one hydrochloride (4f). Yield 80%; mp >250 °C; MS (EI) *m/z* 264 (M^+, 16.0), 224 (25.1), 209 (51.4), 197 (100.0); IR (KBr) 1679 cm^{-1} (CO); ^1H NMR (200 MHz, DMSO-d_6) δ 2.60 (t, J = 4.6 Hz, 4H, NCH_2), 3.56 (t, J = 4.6 Hz, 4H, NCH_2), 7.17 (dd, J = 9.2, 2.8 Hz, 1H, ArH), 7.19–7.20 (m, 1H, ArH), 7.90 (d, J = 9.2 Hz, 1H, ArH). Anal. calcd for $C_{12}H_{13}ClN_4O$·HCl: C, 47.86, H, 4.69, N, 18.60. Found: C, 47.59, H, 4.77, N, 18.73.

6-Methyl-2-(4-methyl-piperazin-1-yl)-3H-quinazolin-4-one (4g). Yield 71%; mp >250 °C; MS (EI) *m/z* 258 (M^+, 68.3), 201 (24.0), 188 (100.0); IR (KBr) 1676.0 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$) δ 2.38 (s, 3H, NCH_3), 2.41 (s, 3H, CH_3), 2.59 (t, J = 4.6 Hz, 4H, NCH_2), 3.75 (t, J = 4.6 Hz, 4H, NCH_2), 7.41–7.42 (m, 1H, ArH), 7.54–7.59 (m, 1H, ArH), 7.86–8.02 (m, 1H, ArH). Anal. calcd for $C_{14}H_{18}N_4O$: C, 65.09, H, 7.02, N, 21.69. Found: C, 65.21, H, 7.15, N, 21.82.

6-Chloro-2-(4-methyl-piperazin-1-yl)-3H-quinazolin-4-one (4h). Yield 77%; mp >250 °C; MS (EI) *m/z* 278 (M^+, 17.90), 221 (10.4), 208 (43.3); IR (KBr) 1679 cm^{-1} (CO); ^1H NMR (200 MHz, DMSO-d_6) δ 2.37 (s, 3H, NCH_3), 2.62 (t, J = 4.6 Hz, 4H, NCH_2), 3.62 (t, J = 4.6 Hz, 4H, NCH_2), 7.26 (d, J = 9.2 Hz, 1H, ArH), 7.53 (dd, J = 9.2, 2.8 Hz, 1H, ArH), 7.81 (d, J = 2.8 Hz, 1H, ArH). Anal. calcd for $C_{13}H_{15}ClN_4O$: C, 56.02, H, 5.42, N, 20.10. Found: C, 56.23, H, 5.56, N, 20.30.

6-Hydroxy-2-(4-methyl-piperazin-1-yl)-3H-quinazolin-4-one (4i). Yield 80%; mp >250 °C; MS (EI) *m/z* 260 (M^+, 19.4), 202 (8.8), 190 (94.8); IR (KBr) 1662 (CO), 3642 cm^{-1} (OH); ^1H NMR (200 MHz, DMSO-d_6) δ 2.24 (s, 3H, NCH_3), 2.45 (t, J = 4.6 Hz, 4H, NCH_2), 3.60 (t, J = 4.6 Hz, 4H, NCH_2), 7.10–7.14 (m, 2H, ArH), 7.25–7.26 (m, 1H, ArH). Anal. calcd for $C_{13}H_{16}N_4O_2$: C, 59.99, H, 6.20, N, 21.52. Found: C, 59.86, H, 6.33, N, 21.40.

4-(4-Oxo-3,4-dihydro-quinazolin-2-yl)piperazine-1-carboxylic acid ethyl ester (4j). Yield 72%; mp >250 °C; MS (EI) *m/z* 302 (M^+, 52.6), 233 (15.1), 199 (13.7), 186 (52.7), 173 (100); IR (KBr) 1598 (CO), 1676 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, J = 4.6 Hz, 3H, CH_3), 3.66 (t, J = 4.6 Hz, 4H, NCH_2), 3.79 (t, J = 4.6 Hz, 4H, NCH_2), 4.14–4.19 (m, 2H, CH_2), 7.19–7.26 (m, 1H, ArH), 7.37 (d, J = 9.2 Hz, 1H, ArH), 7.60–68 (m, 1H, ArH), 8.07 (d, J = 9.2 Hz, 1H, ArH). Anal. calcd for $C_{15}H_{18}N_4O_3$: C, 59.59, H, 6.00, N, 18.53. Found: C, 59.71, H, 6.09, N, 18.67.

6-Methyl-2-pyrrolidin-1-yl-3H-quinazolin-4-one (4k). Yield 86%; mp >250 °C; MS (EI) *m/z* 229 (M^+, 79.2), 201 (48.1), 200 (100.0), 133 (22.8); IR (KBr) 1672 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$) δ 2.02–2.09 (m, 4H, CH_2), 2.39 (s, 3H, CH_3), 3.61 (t, J = 6.66 Hz, 4H, NCH_2), 7.28–7.44 (m, 2H, ArH), 7.86–7.88 (m, 1H, ArH). Anal. calcd for $C_{13}H_{15}N_3O$: C, 68.10, H, 6.59, N, 18.33. Found: C, 68.26, H, 6.43, N, 18.39.

6-Hydroxy-2-pyrrolidin-1-yl-3H-quinazolin-4-one (4l). Yield 79%; mp >250 °C; MS (EI) *m/z* 231 (M^+, 93.7), 202 (100.0), 161 (14.1), 135 (18.3); IR (KBr) 1673 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$ and DMSO-d_6) δ 2.01–2.03 (m, 4H, CH_2), 3.57 (t, J = 6.66 Hz, 4H, NCH_2), 7.13 (dd, J = 9.2, 2.8 Hz, 1H, ArH), 7.26 (d, J = 9.2 Hz, 1H, ArH), 7.47 (d, J = 2.8 Hz, 1H, ArH), 8.90 (brs, 1H, OH). Anal. calcd for $C_{12}H_{13}N_3O_2$: C, 62.23, H, 5.67, N, 18.17. Found: C, 62.40, H, 5.79, N, 18.30.

6-Acetoxy-2-pyrrolidin-1-yl-3H-quinazolin-4-one (4m). Yield 81%; mp >250 °C; MS (EI) *m/z* 273 (M^+, 18.3), 230 (100.0), 229 (36.2), 202 (86.0); IR (KBr) 1666.0 (CO), 1757 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$) δ 2.03–2.04 (m, 4H, CH_2), 2.31 (s, 3H, CH_3), 3.61 (t, J = 6.66 Hz, 4H, NCH_2), 7.28–7.36 (m, 2H, ArH), 7.74 (d, J = 2.8 Hz, 1H, ArH). Anal. calcd for $C_{14}H_{15}N_3O_3$: C, 61.53, H, 5.53, N, 15.38. Found: C, 61.44, H, 5.71, N, 15.25.

6-Chloro-2-pyrrolidin-1-yl-3H-quinazolin-4-one (4n). Yield 89%; mp >250 °C; MS (EI) *m/z* 249 (M^+, 95.0), 222 (52.0), 219 (100.0), 195 (35.5); IR (KBr) 1676 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$) δ 2.04–2.11 (m, 4H, CH_2), 3.62 (t, J = 6.66 Hz, 4H, NCH_2), 7.31 (d, J = 9.2 Hz, 1H, ArH), 7.49 (dd, J = 9.2, 2.8 Hz, 1H, ArH), 8.08 (d, J = 2.8 Hz, 1H, ArH). Anal. calcd for $C_{12}H_{12}ClN_3O$: C, 57.72, H, 4.84, N, 16.83. Found: C, 57.96, H, 4.72, N, 16.70.

7-Chloro-2-pyrrolidin-1-yl-3H-quinazolin-4-one (4o). Yield 77%; mp >250 °C; MS (FAB) 250 (M^+ +1, 100.0); IR (KBr) 1683 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$) δ 2.07–2.08 (m, 4H, CH_2), 3.65 (t, J = 6.66 Hz, 4H, NCH_2), 7.06 (dd, J = 9.2, 2.8 Hz, 1H, ArH), 7.27 (d, J = 2.8 Hz, 1H, ArH), 7.96 (dd, J = 9.2, 2.8 Hz, 1H, ArH). Anal. calcd for $C_{12}H_{12}ClN_3O$: C, 57.72, H, 4.84, N, 16.83. Found: C, 57.66, H, 4.89, N, 16.55.

7-Chloro-2-piperadin-1-yl-3H-quinazolin-4-one (4p). Yield 83%; mp 242 °C; MS (EI) *m/z* 263 (M^+, 100.0), 234 (73.1), 208 (39.4); IR (KBr) 1668 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$) δ 1.71–1.72 (m, 6H, CH_2), 3.71–7.20 (m, 4H, NCH_2), 7.06 (dd, J = 9.2, 2.8 Hz, 1H, ArH), 7.36 (d, J = 2.8 Hz, 1H, ArH), 7.94 (d, J = 9.2 Hz, 1H, ArH). Anal. calcd for $C_{13}H_{14}ClN_3O$: C, 59.21, H, 5.35, N, 15.93. Found: C, 59.45, H, 5.61, N, 15.99.

General procedure of 4-*sec*-amino-2-chloroquinazolines (5a–b)

2,4-Dichloroquinazolines (**2**, 2 mmol) was refluxed for with N^1,N^1-diethyl-pentane-1,4-diamine (4 mmol) in alcohol (5 mL) for 6 h. After completion of the reaction solvent was evaporated under reduced pressure, crude

product obtained was purified on silica gel column chromatography using $CHCl_3$/MeOH (9:1).

N^4-(2,6-Dichloro-quinazolin-4-yl)-N^1,N^1-diethylpentane-1,4-diamine (5a). Yield 72%; mp 90 °C; MS (EI) *m*/*z* 354 (M^+, 7.0), 281 (9.2), 147 (40.7); IR (KBr) 3257 cm^{-1} (NH); ^1H NMR (200 MHz, $CDCl_3$) δ 1.07 (t, $J = 6$ Hz, 6H, CH_3), 1.32 (d, $J = 6$ Hz, 3H, CH_3), 1.67–1.89 (m, 4H, CH_2), 2.51–2.76 (m, 6H, NCH_2), 4.42–4.46 (m, 1H, CH), 7.63–7.67 (m, 2H, ArH), 7.94–7.97 (m, 1H, ArH). Anal. calcd for $C_{17}H_{24}Cl_2N_4$: C, 57.47, H, 6.81, N,15.77. Found: C, 57.54, H, 6.95, N, 15.66.

N^4-(2,7-Dichloro-quinazolin-4-yl)-N^1,N^1-diethylpentane-1,4-diamine (5b). Yield 70%; mp 100 °C; MS (EI) *m*/*z* 354 (M^+, 30), 282 (31.3), 240 (12.9), 197 (12.2); IR (KBr) 3242 cm^{-1} (NH); ^1H NMR (200 MHz, $CDCl_3$) δ 1.03 (t, $J = 6$ Hz, 6H, CH_3), 1.32 (d, $J = 6$ Hz, 3H, CH_3), 1.61–1.77 (m, 4H, CH_2), 2.45–2.62 (m, 6H, NCH_2), 4.44–4.50 (m, 1H, CH), 7.04–7.15 (m, 1H, ArH), 7.35 (dd, $J = 9.2$, 2.8 Hz, 1H, ArH), 7.64–7.78 (m, 1H, ArH). Anal. calcd for $C_{17}H_{24}Cl_2N_4$: C, 57.47, H, 6.81, N,15.77. Found: C, 57.33, H, 6.69, N, 15.65.

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