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A catalyst- and solvent-free selective approach to biologically important quinazolines and benzo[*g*]quinazoline

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Abstract—A solvent-free and catalyst-free approach towards the selective synthesis of quinazolines and benzo[*g*] quinazolines has been developed using conventional microwave oven with excellent yields and reproducibilty.

1. Introduction

Numerous research papers and several review articles have appeared in literature describing in detail the utilization of iminophosphoranes as reagents and intermediates in organic synthesis.[1] The use of iminophosphoranes has now become a powerful gear in organic synthetic strategies directed towards the construction of nitrogen containing heterocycles. The reactions of iminophosphoranes with carbonyl compounds provide an excellent method for the construction of carbon–nitrogen double bonds[2] via inter and intra molecular aza-Wittig reaction. Their application in the preparation of various heterocycles including pyridine derivatives,[2] polycyclic compounds,[3] benzodiazepines[4] and pharmacologically active alkaloids[5] has also been well archived. On the other hand aza-Wittig type reactions of iminophosphoranes with carbon dioxides, carbon disulphides, isocyanates, isothiocyanates and ketenes render access to functionalised heterocumulenes as highly reactive intermediates able to undergo a pleothera of heterocyclization reactions.[6] Recent work in our laboratory[7] has shown the reactions of *N*-imidoyliminophosphoranes with monosubstituted ketenes and diphenyl ketene resulting exclusively in the formation of pyrimidinones via a [4+2] cycloaddition of the initially formed 1,3-diaza-1,3,5-pentatriene and quinazolines via electrocyclic ring closure, respectively.

Quinazolines have demonstrated an increase in potency over other Tyrosine Kinase inhibitors of 4–5 orders of magnitude for the inhibition of isolated Epidermal Growth Factor (EGF) receptor Tyrosine Kinase and 3–4 orders of magnitude for the inhibition of cellular phosphorylation.[8] They have shown remarkable activity as antitubercular,[9] antiviral[10] and anticancer agents.[11] These have been used as DNA ligands[12] and also have shown binding to benzodiazepines and adenosine receptors.[13] Recent disclosures from our laboratory[14] has shown quinazolines with substituents at second and fourth positions to be potent antibacterial agents and further studies are in progress to explore their medicinal and biological use. The growing medicinal importance of these heterocycles perpetuates to provide strong rationale for the development of synthetic methods for their preparation. These efforts have led to several reviews emphasising the synthesis[15] and biological evaluation of quinazolines. The reactions of *N*-imidoyliminophosphoranes with various aldehydes have been shown to result in a mixture of quinazoline and dihydroquinazoline derivatives in a variable ratio depending upon the nature of aldehydes as well as the employed reaction conditions.[16] The reaction apparently suffers from disadvantages such as longer reaction periods (25–90 h), lower yields, lack of selectivity often leading to a mixture of products and cumbersome workup procedure. As part of our continued interest in the chemistry of azadienes,[17] in a recent communication we have developed a simple and advantageous route for the synthesis of quinazoline derivatives using a domestic microwave oven.[18] Several experiments were performed at various power levels in order to establish the optimum reaction conditions. It was assumed that the initially formed 1,3-diazabuta-1,3-dienes **4** underwent electrocyclic ring closure to dihydroquinazoline as intermediates which on aromatisation led to the quinazoline derivatives **3** (Scheme 1). The products were identified as quinazolines **3** on the basis of analytical data and spectral evidences and by comparison of these with reported melting points in literature.

Keywords: Quinazolines; Benzo[*g*]quinazoline; Catalyst-free; Microwave.
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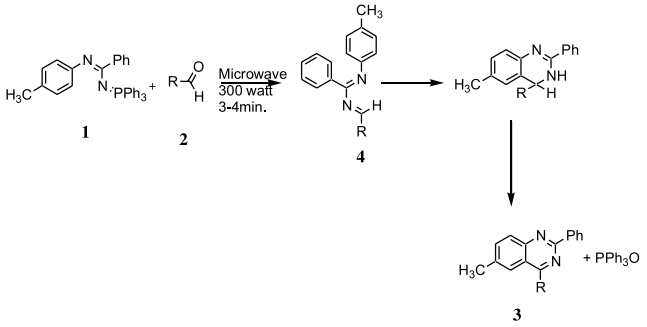


1 2 4 3

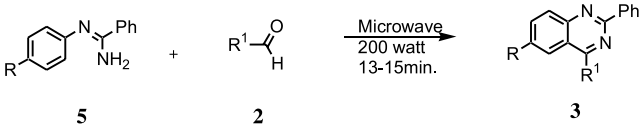
	R	R^1	Yield(%age) (microwave)	Yield(%age) (thermally)
3a	$-CH_3$	C_6H_5	67	--
3b	$-CH_3$	p-O_2N-C_6H_4	64	70
3c	$-CH_3$	p-CH_3O-C_6H_4	59	09
3d	$-CH_3$	p-$Me_2NC_6H_4$	67	--
3e	$-CH_3$	p-Cl-C_6H_4	63	12

Scheme 1.

The spectral evidence involved the absence of a characteristic singlet corresponding to the iminic proton of acyclic 1,3-diazabuta-1,3-diene at $\delta \sim 8.2$ and the absence of characteristic pattern of doublet of doublet of uncyclised *p*-tolyl protons in the ^{1}H NMR spectrum. Interestingly, the formation of dihydroquinazoline derivatives was not observed in reactions of **1** with *para* substituted aromatic aldehydes possessing strong electron donating groups viz. $-OCH_3$ and $-N(CH_3)_2$. This is in contrast to the earlier reports wherein the formation of dihydroquinazoline and their aromatisation was shown to depend on electronic factors.[11] The observed absence of dihydroquinazolines in the present case suggests that the thermal conditions perhaps also play an important role in aromatisation of dihydroquinazolines to quinazolines. The isolation of quinazolines in these reactions still involved their chromatographic separation from triphenylphosphine oxide, resulting in a considerable loss of time and yield.

It was envisaged that this problem may be circumvented by the direct condensation of aldehydes with *N*-arylamidines, without their prior conversion to iminophosphoranes. The reported condensation reactions of *N*-alkylamidines with aldehydes to form 1,3-diazabuta-1,3-dienes invariably employed a Lewis acid catalysts, for example, zinc (II) chloride,[19] titanium(IV) chloride,[20] tin (IV) chloride[21] etc., drastic reaction conditions and cumbersome work up procedures. The stringent reaction conditions employed in these condensation reactions often leading to their irreproducibility[22] and limiting their applicability in organic synthesis. However, there are no literary reports regarding such condensation reactions with *N*-arylamidines even under such adverse reaction conditions.

The reported advantages of microwave assisted reactions[23] prompted us to scrutinize these reactions using a domestic microwave oven and we report herein the solvent-free condensation reactions of *N*-arylamidines **5** with various aldehydes in the absence of any Lewis acid catalyst. Interestingly, these attempts have once again led to the exclusive formation of the desired quinazolines **3** in excellent yields (Scheme 2).

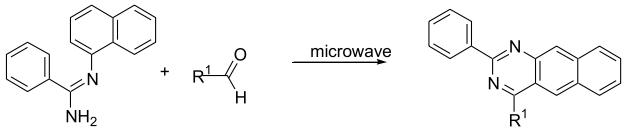


5 2 3

	R	R^1	Yield(%age)
3a	$-CH_3$	C_6H_5	76
3b	$-CH_3$	p-O_2N-C_6H_4	77
3c	$-CH_3$	p-CH_3O-C_6H_4	74
3d	$-CH_3$	p-$Me_2NC_6H_4$	70
3e	$-CH_3$	p-Cl-C_6H_4	73

Scheme 2.

Recently Godde et al. have reported new fluorescent analogs of thymine and cytosine namely benzo[*g*]quinazoline-2,4-(1*H*,3*H*)-dione and (4-amino-1*H*-benzo[*g*]quinazoline-2-one) to probe triple helix formation.[24] When introduced into triplex forming oligonucleotides, this new nucleoside can be used to reveal the protonation state of triplets in triple-stranded structures and thus targets double-stranded DNA through the binding of a short oligonucleotide to homo-purine–homopyrimidine sequences via Hoogsteen (or reverse Hoogsteen) hydrogen bonding.[25,26] Taking this into account, the above methodology has been succesfully extended to the synthesis of benzo[*g*]quinazoline derivatives by carrying out the condensation reactions of *N*-Naphthalen-1-yl-benzamidine[†] with various aldehydes (Scheme 3).



6 7

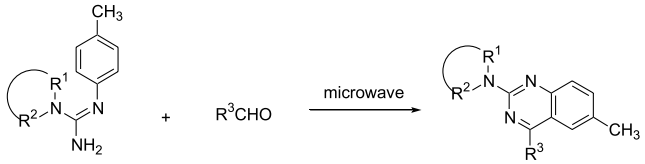
	R^1	%age yield
7a	$-C_6H_5$	72
7b	p-O_2N-C_6H_4	76
7c	p-CH_3O-C_6H_4	78
7d	p-$Me_2NC_6H_4$	80
7e	p-Cl-C_6H_4	72

Scheme 3.

Quinazoline derivatives having a secondary amino functionality at C-2 constitute an important class of medicinal entities acting as α_1 receptor antagonists and antihypertensive agents[27] and the important members include Prazosin and Doxazosin. Prazosin is a prototype of an α_1 receptor antagonist which selectively blocks post synaptic α_1-receptors while having no effects on presynaptic α_2 receptors responsible for the inhibition of norepinephrine release from sympathetic nerve terminals. The compound has been shown to function as a multidrug resistance (MDR) reversal agent and binds to *p*-glycoprotein, a transmembrane transport protein. In view of the above, the present methodology was further extended to the condensation reactions of guanidines **8** with aldehydes resulting once

[†] The preparations should be carried out in an efficient fume cupboard because of highly carcinogenic nature of napthylamine.

again in the exclusive formation of the corresponding 2-*sec*-amino substituted quinazoline derivatives **9** (Scheme 4).



8 **9**

	R^1---------R^2	R^3	Yield (%age)
9a	$(CH_2)_2$-O-$(CH_2)_2$	-C_6H_5	78
9b	$(CH_2)_2$-O-$(CH_2)_2$	*p*-O_2N-C_6H_4	81
9c	$(CH_2)_2$-O-$(CH_2)_2$	*p*-CH_3O-C_6H_4	83
9d	$(CH_2)_2$-O-$(CH_2)_2$	*p*-$(CH_3)_2$-N -C_6H_4	72
9e	$(CH_2)_2$-O-$(CH_2)_2$	*p*-Cl-C_6H_4	78
9f	-----$(CH_2)_4$-----	-C_6H_5	80
9g	-----$(CH_2)_4$-----	*p*-O_2N-C_6H_4	83
9h	-----$(CH_2)_4$----	*p*-CH_3O-C_6H_4	84
9i	-----$(CH_2)_4$-----	*p*-$(CH_3)_2$-N-C_6H_4	74
9*j*	-----$(CH_2)_4$-----	*p*-Cl-C_6H_4	77
9k	------$(CH_2)_5$-----	-C_6H_5	80
9l	------$(CH_2)_5$-----	*p*-O_2N-C_6H_4	84
9m	------$(CH_2)_5$-----	*p*-CH_3O-C_6H_4	78
9n	------$(CH_2)_5$-----	*p*-$(CH_3)_2$-N -C_6H_4	73
9o	------$(CH_2)_5$-----	*p*-Cl-C_6H_4	78

Scheme 4.

Though the reactions reported herein were carried out in a conventional microwave oven, the results were reproducible with excellent yields. Thus, a very simple, convenient, accelerated, less expensive, generalised and high yielding protocol for the selective synthesis of quinazolines and benzo[*g*]quinazolines has been developed.

2. Experimental

Melting points were determined by open capillary using Veego Precision Digital Melting Point apparatus (MP-D) and are uncorrected. IR spectra were recorded on a Shimadzu D-8001 spectrophotometer. ^{1}H NMR spectra were recorded in deuterochloroform with Bruker AC-E 200 (200 MHz) spectrometers using TMS as internal standard. Chemical shift values are expressed as ppm downfield from TMS and *J* values are in Hz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, m: multiplet, q: quartet and br: broad peak. ^{13}C NMR spectra were also recorded on a Bruker AC-200E (50.4 MHz) spectrometers in deuterochloroform using TMS as internal standard. Mass spectra were recorded on Shimadzu GCMS-QP-2000 mass spectrometer. Elemental analyses were performed on Heraus CHN-O-Rapid Elemental Analyzer. Column chromatography was performed on a silica gel (60–120) mesh or Harrison Research Chromatotron using 2 mm plates (Silica gel 60 PF254).

2.1. Procedure for the condensation reactions of *N*-imidoyliminophosphoranes with aldehydes

In a typical experiment, *N*-imidoyliminophosphorane **1** was mixed with 1.5 equiv of aldehyde **2** and the mixture was exposed to microwave radiation at a power of 300 W for a period of 3–4 min. The purification of the reaction mixture by flash chromatography resulted in the exclusive isolation of quinazolines **3** in good yields (65–80%).

2.2. Procedure for the condensation reactions of *N*-arylbenzamidine/*N*-naphthylamidines/guanidines with aldehydes

The procedure employed the exposure of microwave radiations to a mixture of *N*-arylbenzamidine/*N*-naphthylamidine/guanidines **5/8/6** and aldehyde **2** (power of 200 W for 13–15 min in 6–7 cycles of 2 min each). The progress of the reaction was monitored by thin layer chromatography (TLC). The isolated product in each case was recrystallized using (1:5) dichloromethane–hexane mixture and characterized as quinazoline **3/9** and benzo[*g*]quinazolines **7** on the basis of spectral evidences.

2.2.1. 6-Methyl-2,4-diphenylquinazoline (3a). Mp 226–227 °C, δ_H (200 MHz): 2.52 (s, 3H, –CH_3); 7.58 (m, 11H, ArH): 8.2 (m, 2H, ArH). δ_c (50.4 MHz): 20.8, 120.8, 121.2, 122.5, 122.9, 123.8, 124.0, 125.7, 126.2, 127.0, 128.3, 129.1, 131.0, 135.0, 155.4, 157.8 *m*/*z* 296 (M^+).

2.2.2. 6-Methyl-4-(4′-nitrophenyl)-2-phenylquinazoline (3b). Lit. mp (189–190 °C)[17b] mp 189–190 °C, δ_H (200 MHz): 2.58 (s, 3H, –CH_3); 7.50–7.53 (m, 3H, ArH); 7.74–7.78 (d, 2H, *J*=8.1 Hz, ArH); 8.02–8.08 (m, 3H, ArH); 8.44–8.48 (d, 2H, *J*=8.1 Hz, ArH); 8.61–8.66 (m, 2H, ArH): δ_c (50.4 MHz) 21.9, 121.2, 123.7, 124.2, 128.4, 128.5, 129.2, 130.4, 130.6, 131.0, 136.3, 137.7, 137.9, 143.9, 148.5, 159.5, 165.0. *m*/*z* 341 (M^+).

2.2.3. 6-Methyl-4-(4′-methoxyphenyl)-2-phenylquinazoline (3c). Lit. mp (160–165 °C)[17b] mp 160–161 °C, δ_H (200 MHz): 2.51 (s, 3H, –CH_3); 3.92 (s, 3H, –OCH_3); 7.09–7.13 (d, 2H, *J*=8.7 Hz, ArH); 7.46–7.54 (m, 3H, ArH); 7.66–7.71 (d, 1H, *J*=10.0 Hz, ArH); 7.85–7.90 (m, 3H, ArH); 8.00–8.05 (d, 1H, *J*=10.2 Hz, ArH) 8.64–8.68 (m, 2H, ArH): δ_c (50.4 MHz) 21.8, 55.3, 113.9, 115.5, 121.5, 123.9, 125.6, 126.6, 127.2, 128.4, 128.8, 130.1, 130.5, 135.4, 136.8, 150.6, 159.4, 160.9. *m*/*z* 326 (M^+).

2.2.4. 6-Methyl-4-(4′-*N*-*N*-dimethylaminophenyl)-2-phenylquinazoline (3d). Mp 212–213 °C. Anal. Calcd for $C_{23}H_{21}N_3$: C, 81.38; H, 6.24; N, 12.38. Found C, 81.52; H, 6.35; N, 12.13%: δ_H (200 MHz): 2.58 (s, 3H, –CH_3); 3.33 (s, 6H, –$(NCH_3)_2$); 6.91–6.96 (d, 2H, *J*=10.0 Hz, ArH); 7.55 (m, 3H, ArH); 7.74–7.78 (d, 1H, *J*=8.5 Hz, ArH); 7.90–7.95 (d, 2H, *J*=10.0 Hz, ArH); 8.07(m, 2H, ArH); 8.69 (m, 2H, ArH): δ_c (50.4 MHz): 21.2, 40.3, 120.2, 121.0, 122.7,

123.0, 124.5, 125.2, 126.1, 128.2, 128.8, 130.0, 130.5, 132.3, 132.7, 144.5, 150.8, 154.6. *m/z* 339 (M^+).

2.2.5. 4-(4-Chloro-phenyl)-6-methyl-2-phenyl-quinazoline (3e). Lit. mp (181–183 °C)[17b] mp181–183 °C, δ_H (200 MHz): 2.53 (s, 3H, $-CH_3$); 7.05–7.09 (d, 2H, $J=$ 8.4 Hz, ArH); 7.41–7.47 (m, 3H, ArH); 7.65–7.70 (d, 1H, $J=10$ Hz, ArH); 7.84–7.88 (m, 3H, ArH); 8.02–8.06 (d, 1H, $J=10$ Hz, ArH); 8.60–8.64 (m, 2H, ArH): δ_c (50.4 MHz): 21.2, 120.5, 121.7, 122.2, 123.8, 124.6, 125.0, 125.8, 128.3, 128.8, 130.2, 131.1, 133.2, 135.0, 136.7, 156.8, 160.0. *m/z* 330.5 (M^+).

2.2.6. 2,4-Diphenyl-benzo[*g*]quinazoline (7a). Mp 180–181 °C. Anal. Calcd for $C_{24}H_{16}N_2$: C, 86.72; H, 4.85; N, 8.43. Found C, 86.93; H, 4.57; N, 8.50%: δ_H (200 MHz): 6.88–6.92 (d, 1H, $J=8.4$ Hz, ArH); 7.27–7.59 (m, 11H, ArH); 7.69–7.73 (d, 1H, $J=8.4$ Hz, ArH); 7.95–8.00 (m, 2H, ArH); 8.91–8.95 (d, 1H, $J=8.4$ Hz, ArH): δ_c (50.4 MHz): 118.7, 124.3, 124.4, 124.5, 125.7, 126.0, 126.7, 127.2, 127.4, 128.2, 128.6, 129.0, 129.8, 130.6, 133.7, 135.4, 137.7, 145.6, 152.8, 155.0. *m/z* 332 (M^+).

2.2.7. 4-(4-Nitro-phenyl)-2-phenyl-benzo[*g*]quinazoline (7b). Mp 155–156 °C. Anal. Calcd for $C_{24}H_{15}N_3O_2$: C, 76.38; H, 4.01; N, 11.13. Found: C, 76.28; H, 3.83; N, 11.41%: δ_H (200 MHz): 6.92–6.96 (d, 1H, $J=8.4$ Hz, ArH); 7.36–7.62 (m, 10H, ArH); 7.69–7.73 (d, 1H, $J=8.4$ Hz, ArH); 7.97–8.02 (m, 2H, ArH); 8.93–8.97 (d, 1H, $J=$ 8.4 Hz, ArH) δ_c (50.4 MHz): 117.9, 124.0, 124.7, 125.5, 126.0, 126.3, 126.6, 127.2, 127.4, 128.0, 128.6, 129.9, 130.1, 133.4, 134.4, 137.0, 140.7, 145.6, 152.0, 155.7. *m/z* 377 (M^+).

2.2.8. 4-(4-Methoxy-phenyl)-2-phenyl-benzo[*g*]quinazoline (7c). Mp 167–168 °C. Anal. Calcd for $C_{25}H_{18}N_2O$: C, 82.85; H, 5.01; N, 7.73. Found C,83.05; H, 4.82; N, 7.64%: δ_H (200 MHz): 3.95 (s, 3H, $-OCH_3$); 6.90–6.94 (d, 1H, $J=$ 8.4 Hz, ArH); 7.36–7.62 (m, 10H, ArH); 7.70–7.74 (d, 1H, $J=8.4$ Hz, ArH); 7.97–8.02 (m, 2H, ArH); 8.92–8.96 (d, 1H, $J=8.4$ Hz, ArH) δ_c (50.4 MHz): 55.3 ($-OCH_3$), 118.0, 122.8, 124.0, 125.4, 126.6, 126.9, 127.6, 127.9, 128.4, 128.6, 129.0, 129.9, 130.4, 133.8, 134.6, 137.0, 140.8, 145.3, 153.0, 156.7. *m/z* 362 (M^+).

2.2.9. Dimethyl-[4-(2-phenyl-benzo[*g*]quinazolin-4-yl)-phenyl]-amine (7d). Mp 198–199 °C. Anal. Calcd for $C_{26}H_{21}N_3$:C, 83.17; H, 5.64; N, 11.19. Found C, 83.37; H, 5.51; N, 11.12%: δ_H (200 *MHz*): 2.90 (s, 6H, $-(NCH_3)_2$); 6.88–6.92 (d, 1H, $J=8.2$ Hz, ArH); 7.42–7.70 (m, 10H, ArH); 7.73–7.77 (d, 1H, $J=8.2$ Hz, ArH); 7.93–7.98 (m, 2H, ArH); 8.94–8.98 (d, 1H, $J=8.4$ Hz, ArH) δ_c (50.4 MHz): 43.2 ($-(NCH_3)_2$); 118.2, 122.5, 124.3, 125.7, 126.8, 127.0, 127.4, 127.9, 128.3, 128.6, 129.3, 129.9, 130.8, 134.0, 134.7, 137.3, 140.2, 145.2, 153.7, 156.9. *m/z* 375 (M^+).

2.2.10. 4-(4-Chloro-phenyl)-2-phenyl-benzo[*g*]quinazoline (7e). Mp 156–158 °C. Anal. Calcd for $C_{24}H_{15}N_2Cl$: C, 78.58; H, 4.12; N, 7.64. Found C, 78.67; H, 4.20; N, 7.45: δ_H (200 MHz): 6.88–6.92 (d, 1H, $J=8.4$ Hz, ArH); 7.40–7.60 (m, 10 H, ArH); 7.72–7.76 (d, 1H, $J=8.2$ Hz, ArH); 7.92–7.97 (m, 2H, ArH); 8.94–8.98 (d, 1H, $J=8.4$ Hz, ArH) δ_c (50.4 MHz): 118.4, 124.3, 124.0, 124.5, 125.2, 125.5, 126.3, 127.0, 127.4, 128.1, 128.3, 129.0, 129.6, 130.5, 133.2, 135.4, 137.0, 145.3, 153.0, 155.3. *m/z* 366.5 (M^+).

2.2.11. 6-Methyl-4-phenyl-2-morpholino-4-yl-quinazoline (9a). Mp 147–148 °C. Anal. Calcd for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76. Found C, 74.97; H, 6.38; N, 13.48% δ_H (200 MHz): 2.41 (s, 3H, $-CH_3$); 3.81–3.86 (m, 4H, $-CH_2-N-CH_2-$); 3.98–4.02 (m, 4H, $-CH_2-O-CH_2-$); 7.54–7.62 (m, 6H, ArH); 7.74–7.76 (m, 2H, ArH): δ_c (50.4 MHz) 21.37 ($-CH_3$); 44.56 ($-CH_2-N-CH_2-$); 66.97 ($-CH_2-O-CH_2-$); 117.7, 126.0, 128.3, 128.5, 129.5, 129.7, 130.0, 131.3, 135.7, 137.9, 160.9, 168.7. *m/z* 305 (M^+).

2.2.12. 6-Methyl-2-morpholin-4-yl-4-(4-nitro-phenyl)-quinazoline (9b). Mp 188–189 °C. Anal. Calcd for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.18; N, 15.99. Found C, 65.32; H, 5.27; N, 15.79%: δ_H (200 MHz): 2.40 (s, 3H, $-CH_3$); 3.78–3.84 (m, 4H, $-CH_2-N-CH_2-$); 3.92–3.97 (m, 4H, $-CH_2-O-CH_2-$); 7.70–7.74 (d, 2H, $J=8.1$ Hz, ArH); 8.07–8.12 (m, 3H, ArH); 8.44–8.48 (d, 2H, $J=8.1$ Hz, ArH); δ_c (50.4 MHz): 22.0 ($-CH_3$); 43.6 ($-CH_2-N-CH_2-$); 63.7 ($-CH_2-O-CH_2$); 118.2, 123.5, 124.7, 128.5, 129.3, 130.3, 132.7, 133.8, 134.0, 148.7, 157.5, 163.2. *m/z* 350 (M^+).

2.2.13. 4-(4-Methoxy-phenyl)-6-methyl-2-morpholin-4-yl-quinazoline (9c). Mp 182–183 °C. Anal. Calcd for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found C, 71.76; H, 6.48; N, 12.26%: δ_H (200 MHz): 2.41 (s, 3H, $-CH_3$); 3.81–3.86 (m, 4H, $-CH_2-N-CH_2$); 3.92 (s, 3H, $-OCH_3$); 3.98–4.02 (m, 4H, $-CH_2-O-CH_2-$); 7.08–7.12 (d, 2H, $J=8.2$ Hz, ArH); 7.66–7.71 (d, 1H, $J=10.2$ Hz, ArH); 7.85–7.90 (m, 3H, ArH); 8.01–8.06 (d, 1H, $J=10.3$ Hz, ArH): δ_c (50.4 MHz): 20.8 ($-CH_3$); 42.8 ($-CH_2-N-CH_2-$); 55.0 ($-OCH_3$); 66.9($-CH_2-O-CH_2-$); 118.0, 119.2, 120.8, 121.4, 123.5, 124.7, 125.0, 128.5, 133.0, 144.7, 152.7, 155.8. *m/z* 335 (M^+).

2.2.14. 6-Methyl-4-(4′-*N*-*N*-dimethylaminophenyl)-2-morpholin-4-yl-quinazoline (9d). Mp 198–199 °C. Anal. Calcd for $C_{21}H_{24}N_4O$: C, 72.39; H, 6.94; N, 16.08. Found C, 72.79; H, 6.48; N, 16.18%: δ_H (200 MHz): 2.45 (s, 3H, $-CH_3$); 2.98 (s, 6H, $-N(CH_3)_2$); 3.80–3.85 (m, 4H, $-CH_2-N-CH_2-$); 3.99–4.03 (m, 4H, $-CH_2-O-CH_2-$); 6.84–6.88 (d, 2H, $J=8.5$ Hz, ArH); 7.43–7.48 (d, 1H, $J=10.0$ Hz, ArH); 7.53–7.58 (d, 1H, $J=10.0$ Hz); 7.74–7.78 (m, 3H, ArH): δ_c (50.4 MHz): 21.2 ($-CH_3$); 40.3 ($-N(CH_3)_2$); 43.6 ($-CH_2-N-CH_2-$); 54.0 ($-CH_2-O-CH_2-$); 120.2, 121.9, 122.0, 123.5, 124.8, 125.7, 128.2, 130.2, 131.7, 142.7, 153.5, 157.5. *m/z* 348 (M^+).

2.2.15. 4-(4-Chloro-phenyl)-6-methyl-2-morpholin-4-yl-quinazoline (9e). Mp 180–181 °C. Anal. Calcd for $C_{19}H_{18}N_3OCl$: C, 67.15; H, 5.34; N, 12.37. Found C, 67.03; H, 5.71; N, 12.21%: δ_H (200 MHz): 2.42 (s, 3H, $-CH_3$); 3.80–3.85 (m, 4H, $-CH_2-N-CH_2-$); 3.92–3.97 (m, 4H, $-CH_2-O-CH_2-$); 7.12–7.16 (d, 2H, $J=8.4$ Hz, ArH); 7.57–7.62 (m, 3H, ArH); 7.84–7.88 (d, 2H, $J=8.4$ Hz, ArH): δ_c (50.4 MHz): 20.7 ($-CH_3$); 43.8 ($-CH_2-N-CH_2-$); 64.9 ($-CH_2-O-CH_2-$); 119.0, 122.3, 123.4, 124.3, 126.2, 126.8, 129.7, 130.8, 131.2, 134.8, 154.7, 157.2. *m/z* 339.5 (M^+).

2.2.16. 6-Methyl-4-phenyl-2-pyrrolidin-1-yl-quinazoline (9f). Mp 140–141 °C. Anal. Calcd for $C_{19}H_{19}N_3$: C, 78.86; H, 6.62; N, 14.52. Found C, 79.02; H, 6.68; N, 14.28%: δ_H (200 MHz): 2.01–2.07 (m, 4H, $-CH_2-CH_2-$); 2.37 (s, 3H, $-CH_3$); 3.70–3.76 (m, 4H, $-CH_2-N-CH_2-$); 7.50–7.58 (m, 6H, ArH); 7.70–7.73 (m, 2H, ArH); δ_c (50.4 MHz): 21.1 ($-CH_3$); 24.9 ($-CH_2-CH_2-$); 45.7 ($-CH_2-N-CH_2$); 117.3, 118.2, 120.1, 122.5, 123.3, 125.4, 127.7, 130.2, 135.6, 145.1, 157.9, 166.6. *m/z* 289 (M^+).

2.2.17. 6-Methyl-4-(4-nitro-phenyl)-2-pyrrolidin-1-yl-quinazoline (9g). Mp 154–155 °C. Anal. Calcd for $C_{19}H_{18}N_4O_2$: C, 68.25; H, 5.43; N, 16.76. Found C, 68.48; H, 5.20; N, 16.86%: δ_H (200 MHz): 1.82–1.86 (m, 4H, $-CH_2-N-CH_2-$); 2.37 (s, 3H, $-CH_3$); 3.72–3.77 (m, 4H, $-CH_2-N-CH_2-$); 7.70–7.74 (d, 2H, $J=8.2$ Hz, ArH); 8.01–8.07 (m, 3H, ArH); 8.44–8.48 (d, 2H, $J=8.2$ Hz, ArH): δ_c (50.4 MHz): 22.0 (–CH3); 26.2 ($-CH_2-CH_2-$); 48.1 ($-CH_2-N-CH_2-$); 118.2, 119.1, 120.0, 120.8, 123.4, 126.2, 128.5, 130.0, 131.8, 142.7, 153.5, 156.0. *m/z* 334 (M^+).

2.2.18. 6-Methyl-4-(4′-methoxyphenyl)-2-pyrrolidino-1-yl-quinazoline (9h). Mp 147–148 °C. Anal. Calcd for $C_{21}H_{24}N_3O$: C, 75.21; H, 6.63; N, 13.16. Found C, 75.03; H, 6.73; N, 13.12%: δ_H (200 MHz): 2.00–2.07 (m, 4H, $-CH_2-CH_2-$); 2.40 (s, 3H, $-CH_3$); 3.73–3.79 (m, 4H, $-CH_2-N-CH_2-$); 3.92 (s, 3H, $-OCH_3$); 7.03–7.08 (d, 2H, ArH, $J=8.8$ Hz); 7.49–7.64 (m, 3H, ArH); 7.71–7.76 (d, 2H, ArH, $J=8.8$ Hz): δ_c (50.4 MHz): 21.3 ($-CH_3$); 25.5 ($-CH_2-CH_2-$); 47.2 ($-CH_2-N-CH_2$); 55.2 ($-OCH_3$); 113.7, 117.0, 124.6, 126.2, 127.5, 128.7, 130.2, 131.4, 135.6, 150.1, 160.9, 168.6. *m/z* 319 (M^+).

2.2.19. Dimethyl-[4-(6-methyl-2-pyrrolidin-1-yl-quinazolin-4-yl)-phenyl]-amine (9i). Mp 164–165 °C. Anal. Calcd for $C_{21}H_{24}N_4$: C, 75.87; H, 7.28; N, 16.85. Found C, 76.02; H, 7.48; N, 16.43%: δ_H (200 MHz): 2.02–2.06 (m, 4H, $-CH_2-CH_2-$); 2.32 (s, 3H, $-CH_3$); 2.98 (s, 6H, $-N(CH_3)_2$); 3.68–3.73 (m, 4H, $-CH_2-N-CH_2-$); 6.94–6.98 (d, 2H, $J=8.4$ Hz, ArH); 7.52–7.57 (d, 1H, $J=10.2$ Hz, ArH); 7.64–7.69 (d, 1H, $J=10.2$ Hz, ArH); 7.90–7.95 (m, 3H, ArH): δ_c (50.4 MHz): 22.0 ($-CH_3$); 23.8 ($-CH_2-CH_2-$); 39.4 ($-N(CH_3)_2$); 42.7 ($-CH_2-N-CH_2-$); 118.0, 119.2, 123.4, 124.5, 127.2, 128.0, 129.3, 130.1, 132.5, 143.5, 150.7, 157.2. *m/z* 332 (M^+).

2.2.20. 4-(4-Chloro-phenyl)-6-methyl-2-pyrrolidin-1-yl-quinazoline (9J). Mp 157–158 °C. Anal. Calcd for $C_{19}H_{18}N_3Cl$: C, 70.47; H, 5.60; N, 12.98. Found C, 70.86; H, 5.39; N, 12.87%: δ_H (200 MHz): 2.04–2.08 (m, 4H, $-CH_2-CH_2-$); 2.24 (s, 3H, $-CH_3$); 3.64–3.70 (m, 4H, $-CH_2-N-CH_2-$); 6.90–6.94 (d, 2H, $J=8.4$ Hz, ArH); 7.51–7.56 (d, 1H, $J=10.2$ Hz, ArH); 7.64–7.69 (d, 1H, $J=10.2$ Hz, ArH); 7.85–7.90 (m, 3H, ArH): δ_c (50.4 MHz): 20.2 ($-CH_3$); 23.4 ($-CH_2-CH_2-$); 42.7 ($-CH_2-N-CH_2-$); 118.4, 119.0, 122.4, 124.7, 126.2, 128.3, 129.0, 130.1, 133.5, 143.5, 150.9, 156.2. *m/z* 323.5 (M^+).

2.2.21. 6-Methyl-4-phenyl-2-piperidin-1-yl-quinazoline (9k). Mp 137–138 °C. Anal. Calcd for $C_{20}H_{21}N_3$: C, 79.17; H, 6.98; N, 13.85. Found C, 79.28; H, 6.83; N, 13.89%: δ_H (200 MHz): 1.72–1.77 (m, 6H, $-CH_2-CH_2-CH_2-$); 2.38 (s, 3H, $-CH_3$); 3.97–4.02 (m, 4H, $-CH_2-N-CH_2-$); 7.50–7.58 (m, 6H, ArH); 7.70–7.74 (m, 2H, ArH): δ_c (50.4 MHz): 19.3 ($-CH_3$); 25.2 ($-CH_2$); 26.0 ($-CH_2-CH_2-$); 44.4 ($-CH_2-N-CH_2-$); 117.0, 118.3, 120.4, 122.7, 123.4, 125.2, 127.9, 130.0, 135.3, 145.3, 157.7, 166.3. *m/z* 303 (M^+).

2.2.22. 6-Methyl-4-(4-nitro-phenyl)-2-piperidin-1-yl-quinazoline (9l). Mp 160–162 °C. Anal. Calcd for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found C, 68.80; H, 5.87; N, 15.96%: δ_H (200 MHz): 1.70–1.75 (m, 6H, $-CH_2-CH_2-CH_2-$); 2.41 (s, 3H, $-CH_3$); 3.98–4.03 (m, 4H, $-CH_2-N-CH_2-$); 7.70–7.74 (d, 2H, $J=8.2$ Hz, ArH); 8.02–8.08 (m, 3H, ArH); 8.44–8.48 (d, 2H, $J=8.2$ Hz, ArH): δ_c (50.4 MHz): 19.3 ($-CH_3$); 25.2 ($-CH_2$); 26.0 ($-CH_2-CH_2-$); 44.4 ($-CH_2-N-CH_2-$); 118.0, 123.5, 124.4, 128.7, 129.2, 130.4, 132.8, 133.9, 134.3, 148.5, 157.3, 163.0. *m/z* 348 (M^+).

2.2.23. 4-(4-Methoxy-phenyl)-6-methyl-2-piperidin-1-yl-quinazoline (9m). Mp 140–141 °C. Anal. Calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60. Found C, 75.47; H, 6.98; N, 12.78%: δ_H (200 MHz): 1.70–1.75 (m, 6H, $-CH_2-CH_2-CH_2-$); 2.37 (s, 3H, $-CH_3$); 3.90 (s, 3H, $-OCH_3$); 3.98–4.03 (m, 4H, $-CH_2-N-CH_2-$); 6.88–6.92 (d, 2H, $J=8.2$ Hz, ArH); 7.38–7.43 (d, 1H, $J=10.3$ Hz, ArH); 7.52–7.57 (d, 1H, $J=10.3$ Hz, ArH); 7.75–7.79 (m, 3H, ArH): δ_c (50.4 MHz): 19.7 ($-CH_3$); 25.0 ($-CH_2$); 25.9 ($-CH_2-CH_2-$); 44.8 ($-CH_2-N-CH_2-$); 55.0 ($-OCH_3$); 119.8, 120.7, 121.2, 122.7, 123.0, 124.5, 127.8, 132.8, 133.0, 145.0, 152.4, 157.4 *m/z* 333 (M^+).

2.2.24. 6-Methyl-4-(4′-*N*-*N*-dimethylaminophenyl)-2-piperidin-1-yl-quinazoline (9n). Mp 143–144 °C. Anal. Calcd for $C_{22}H_{26}N_4$: C, 76.27; H, 7.56; N, 16.17. Found C, 76.43; H, 7.72; N, 15.93%: δ_H (200 MHz): 1.70–1.75 (m, 6H, $-CH_2-CH_2-CH_2-$); 2.41 (s, 3H, $-CH_3$); 2.93 (s, 6H, $-N(CH_3)_2$); 3.98–4.03 (m, 4H, $-CH_2-N-CH_2-$); 6.84–6.88 (d, 2H, $J=8.2$ Hz, ArH); 7.43–7.48 (d, 1H, $J=10.3$ Hz, ArH); 7.53–7.58 (d, 1H, $J=10.3$ Hz, ArH); 7.74–7.78 (m, 3H, ArH) δ_c (50.4 MHz): 21.3 ($-CH_3$); 25.0 ($-CH_2$); 25.7, ($-CH_2-CH_2-$); 39.3 ($-N(CH_3)_2$); 44.9 (CH_2-N-CH_2-); 118.5, 119.3, 120.2, 125.6, 125.8, 126.3, 130.8, 131.3, 134.9, 146.3, 154.3, 158.7. *m/z* 346 (M^+).

2.2.25. 4-(4-Chloro-phenyl)-6-methyl-2-piperidin-1-yl-quinazoline (9o). Mp 156–157 °C. Anal. Calcd for $C_{20}H_{20}N_3Cl$: C, 71.10; H, 5.97; N, 12.44. Found C, 71.03; H, 6.04; N, 12.51%: δ_H (200 MHz): 1.69–1.75 (m, 6H, $-CH_2-CH_2-CH_2-$); 2.41 (s, 3H, $-CH_3$); 3.98–4.02 (m, 4H, $-CH_2-N-CH_2-$); 6.90–6.94 (d, 2H, $J=8.2$ Hz, ArH); 7.43–7.48 (d, 1H, $J=10.3$ Hz, ArH); 7.57–7.62 (d, 1H, $J=10.3$ Hz, ArH); 7.74–7.78 (m, 3H, ArH) δ_c(50.4 MHz): 21.3 ($-CH_3$); 25.0 ($-CH_2$); 25.7, ($-CH_2-CH_2-$); 44.2 (CH_2-N-CH_2-); 118.0, 119.3, 120.5, 123.6, 125.8, 126.7, 130.0, 131.2, 133.9, 147.3, 154.3, 158.7. *m/z* 337.5 (M^+).

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