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## Graphical Abstract

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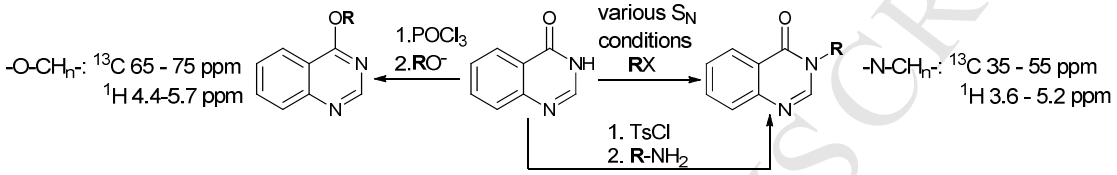

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# The Unambiguous Synthesis and NMR Assignment of 4-Alkoxy and 3-Alkylquinazolines

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ABSTRACT

Contrary to a number of reports, alkylations of the privileged 3,4-dihydroquinazoline scaffold provide *N*3-alkylated products, and not 4-alkoxyquinazolines. To correctly assign the structure, $^{13}$C NMR shifts of the –Z–$CH_n$– (Z = O, N) fragment are necessary; resonances in the 45-55 ppm range are indicative of *N*3-alkylation. Treatment of 3,4-dihydroquinazoline-4-one with *p*-TsCl afforded the *N*3-tosylated compound, whose reaction with an amine yielded the corresponding *N*3-alkyl derivative. A mechanism corroborated by $^{15}$N-labeling involving pyrimidine ring opening and recyclisation is proposed. Finally, the unambiguous preparation of 4-alkoxyquinazolines is described via treatment of 3,4-dihydroquinazoline-4-ones with $PCl_5$ followed by an alkoxide.



## Introduction

Simple modifications of heterocyclic structures have consistently afforded novel pharmaceuticals. $S_N$ reactions are particularly well suited for the modification of nucleophilic sites in many heterocycles. However, when there are two or more alkylation sites, the formation of regioisomers with similar $^1$H NMR spectra is often encountered. The relative simplicity of the derivatives is seductive, however, and often results in less than rigorous NMR analysis being carried out that leads to erroneous assignments which are ultimately perpetuated throughout the literature. During the course of our investigation on the alkylation of the 3,4-dihydroquinazoline-4-one scaffold, we encountered numerous errors and discrepancies of the ensuing medicinally important quinazoline derivatives. To better understand the reasons behind these equivocal literature reports, we thoroughly re-examined the simple alkylation and sulfonylation of 3,4-dihydroquinazoline-4-one using $^{15}$N labeling.

The 3,4-dihydroquinazoline-4-one scaffold (**1**, Fig. 1) is a privileged substructure present in a number of biologically important compounds.[1] Its derivatives include 2-substituted compounds, such as methaqualone, a well-known sedative and hypnotic, chrysogine, the antimalarials (+)-febrifugine and (+)-isofebrifugine isolated from the plant *Dichora febrifuga*, and fused ring systems like (-)-vasicinone that possess bronchodilatory activity.[1] In recent years, numerous reports[2] and patents[3] on the biological activity of compounds incorporating the closely related 4-oxyquinazoline fragment (**2**) have been published. These compounds have subsequently been evaluated as possible lymphocyte potassium channel Kv1.3 blockers,[2b] inhibitors of protein kinases[3a] and caspases,[2c] and adenosine $A_{2A}$ receptor antagonists.[2d] Some 4-oxyquinazolines have also been reported to be anti-infectives[2e] and cytostatics,[2a] while others have shown promise for diabetes and obesity.[3b] In all cases, classical $S_N$ reactions of 3,4-dihydroquinazoline-4-ones (**3**) were used to introduce the 4-alkoxy function (*vide infra*).

3,4-Dihydroquinazoline-4-ones have three potential alkylation sites, i.e., the N1, N3 and the OH groups (Fig. 1). Not unexpectedly, a number of $S_N$ procedures have been published (*vide infra*), leading to *N*3- (**4**) and/or *O*-alkylation (**5**). However, it was not always clear why one derivative was reportedly formed in preference to another under very similar conditions. Indeed, contradictory reports regarding the formation of either *N*3- or *O*-alkylated derivatives from virtually the same substrates under nearly identical conditions are not infrequent.

Alkylations of various 3,4-dihydroquinazoline-4-ones[2a,2e,3c,4] largely employ compounds containing **a substituent at C2** of the quinazoline ring. The formation of mixtures of both *O*- and *N*3-alkylated products depends on the electronic and steric nature of the C2 substituent and the prevailing reaction conditions. By way of example, Burbuliene et al. reported[4b] that the alkylation of 2-methylsulfanyl-3,4-dihydroquinazoline-4-one with α-halocarbonyl compounds can be directed with 100 % selectivity towards *O*- or *N*3-alkylated product at room

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temperature or reflux, respectively. Several patents[3c,3d,3e] have indicated the use of an alcohol under Mitsunobu conditions or alkyl bromide/$K_2CO_3$ in DMF at room temperature[3b] to be selective for *O*-alkylation. While these findings seem to indicate

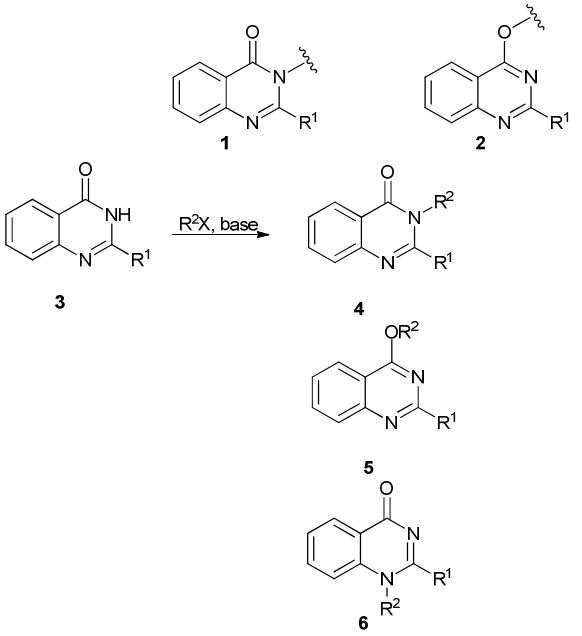


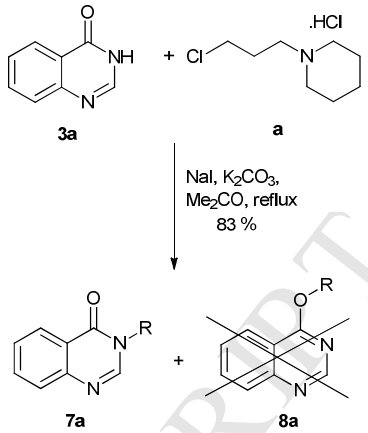

**Figure 1.** Alkylation sites in 3,4-dihydroquinazoline-4-ones

that thermodynamic conditions and low C2 steric hindrance should favor *N*-alkylation, El-Subbagh et al. claim to have prepared[2a] a series of 6-iodo-2-(2-thienyl)-4-alkoxyquinazolines following treatment of 6-iodo-2-(2-thienyl)-3,4-dihydroquinazoline-4-one with ethyl bromoacetate at reflux for 12 hours.

2-Unsubstituted 3,4-dihydroquinazolines (i.e., $R^1$ = H) were converted into 4-alkoxy derivatives upon treatment with RBr/KI/base in $CHCl_3$/reflux[5] (single example), RBr in MeCN/reflux,[2b] MeI/NaH in DMF/rt[3a] ROMs/NaH in DMF/100 °C,[2d] RBr/KF/NaI in DMF,[2c] with an alcohol under Mitsunobu conditions[3c] or the same (ROH) in the presence of BOP and $Cs_2CO_3$.[6] Surprisingly, the formation of *N*3-alkylated products has been described using nearly identical conditions, namely RI/NaH in DMF under MW irradiation[7a] and at room temperature,[7b] or via the epoxide/KOH in MeOH/reflux.[7c] Clearly, reports on alkylations of 3,4-dihydroquinazoline-4-one are ambiguous at best, and contradictory at worst. Even though *N*3-alkylated products can also be unambiguously prepared upon treatment of 3,4-dihydroquinazoline-4-one with amines in the presence of HATU/DBU[8a] or by using the Mukaiyama reagent/DIPEA,[8b] (via a mechanism involving amine attack on the 4-oxo group followed by temporary opening of the pyrimidine ring) classical $S_N$ alkylations still constitute a less costly alternative.

**Results and Discussion**

We encountered the confusing literature reports while attempting to prepare a series of compounds containing the 4-oxyquinazoline moiety (**2**) for potential bronchodilatory activity. Thus, when 3,4-dihydroquinazoline-4-one (**3a**) was treated with 1-(3-chloropropyl)piperidine hydrochloride (**a**) under $S_N$ conditions, we obtained a single product in 83% yield, the $^1$H NMR spectrum of which agreed well with that expected for the desired *O*-alkylated compound **8a**, since the $^1$H NMR chemical shift of the –Z–$CH_2$– (Z = O or N) protons was 4.06 ppm (Scheme 1).




**Scheme 1.** Alkylation of 3,4-dihydroquinazoline-4-one (**3a**)

However, a HSQC experiment revealed that these protons correlated to a $^{13}$C resonance at 46.6 ppm. A more detailed 2D NMR analysis (Fig. 2) confirmed that the *N*3-alkylated species **7a** had, in fact, formed.

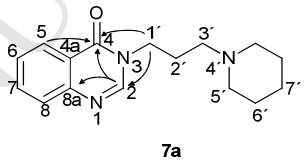
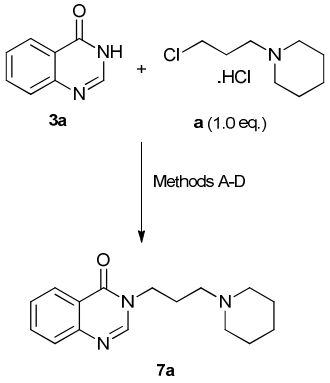



**Figure 2.** HMBC connectivities in **7a**

Substrate **3a** was subsequently exposed to alkylating agent **a** under various conditions including classical $S_N$ reactions (methods A, C, D) or phase-transfer (B) reactions (Scheme 2) involving both room temperature and reflux. In all cases, the only detected product was *N*3-alkylated quinazolinone **7a** even though literature method (C) was described as being selective for *O*-alkylation.[3a,3b]

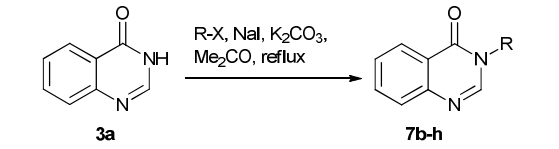



**Scheme 2.** $S_N$ reactions attempted in the alkylation of **3a**

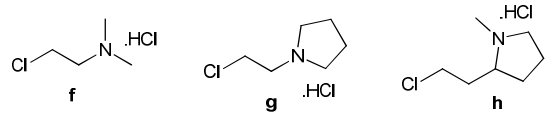
Previous literature reports employing the Mitsunobu reaction[3c,3d,3e,9] indicated that *O*-alkylation was the major/exclusive product. However, the reaction of quinazolinone **3a** and 3-(piperidine-1-yl)propanol under classic Mitsunobu conditions[3d] afforded a mixture of *N*3- and *O*-alkylated species

**7a** and **8a** (see also Scheme 7 for **8a**) in 60% and 29% yield, respectively.

Compound **3a** was next treated with a series of alkylating agents (Scheme 3) under simple conditions using RX/NaI/$K_2CO_3$ at reflux in acetone. As evident from Scheme 3 and Table 1, high yields of *N*3-alkylated products, the structures of which were unequivocally confirmed by 2D NMR, were obtained. Most importantly, the data in Table 1 show that **only $^{13}$C shifts of the -Z–CH$_n$– carbon (C1´, see Fig. 2) can serve as a reliable criterion of *O*- or *N*3-alkylation**. While $^1$H chemical shifts do not exclude *O*-alkylation, $^{13}$C resonances below 50 ppm are typical of *N*-alkylation (see also Tables 2 and 3 for examples of $^{13}$C shifts of *O*-alkylated products). Using solvents other than $CD_3OD$ does not change this general observation since, for example, the C1´ resonance of compound **7d** was 49.0 ppm in DMSO and 49.6 ppm in $CDCl_3$.




R-X: **b** $CH_3$-I, **c** $CH_3CH_2CH_2$-Br, **d** $PhCH_2$-Br, **e** Br-$CH_2$-COOH

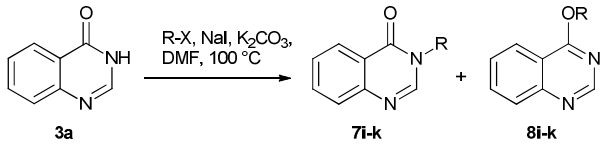



**Scheme 3.** Alkylation of **3a** with various primary halides

**Table 1.** $^1$H- and $^{13}$C-NMR chemical shifts in $CD_3OD$ of C(1') group and the yields of compounds **7a**-**h**

| Compound | δH (ppm) | δC (ppm) | Isolated yield (%) |
|---|---|---|---|
| **7a** | 4.06 | 46.6 | 83 |
| **7b** | 3.58 | 34.5 | 95 |
| **7c** | 3.98 | 49.6 | 89 |
| **7d** | 5.23 | 50.7 | 91 |
| **7e** | 4.81 | 48.4 | 90 |
| **7f** | 4.18 | 45.2 | 90 |
| **7g** | 4.16 | 46.3 | 96 |
| **7h** | 4.06 | 45.7 | 89 |

Only alkylation with propyl bromide (**c**), afforded trace amounts of the *O*-alkylated product (≤ 3 %) in the crude reaction mixture. In this case, the peak corresponding to C1´ was observed at 70.1 ppm, and the corresponding protons appeared at 4.49 ppm in $CD_3OD$. We next evaluated the influence of alkyl branching on the product distribution. The reaction with *i*-PrBr was extremely slow at reflux in acetone, but did yield two products, the major one being the *N*3-alkylated derivative. Changing the solvent to DMF accelerated the reaction, with negligible influence on product ratio, and afforded **7i** in 66% isolated yield (Scheme 4, Table 2). Importantly, when the *O*-isopropyl isomer **8i** was resubjected to the same reaction conditions for 24 hours, no rearrangement to **7i** was observed indicating the reaction is under kinetic control, and the ratio of both products is governed by their relative rates of formation.




R-X: **i** $(CH_3)_2$CH-Br, **j** $(CH_3)_2CHCH_2$-Br, **k** $CH_3CH(Br)CH_2CH_3$

**Scheme 4.** Alkylation of **3a** with secondary/branched halides

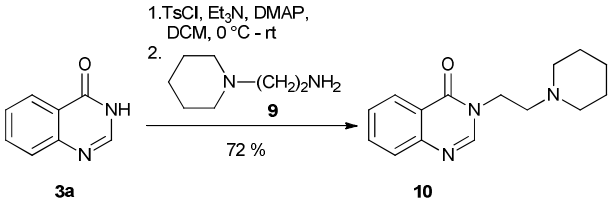
**Table 2.** $^1$H- and $^{13}$C-NMR chemical shifts in $CD_3OD$ of C1' and the yields of compounds **7i**-**k** and **8i**-**k**

| Compound: | δH (ppm) | δC (ppm) | Isolated yield (%) |
|---|---|---|---|
| **7i** | 5.07 | 48.4 | 66 |
| **8i** | 5.65 | 72.1 | 18 |
| **7j** | 3.83 | 54.9 | 75 |
| **8j** | 4.41 | 74.6 | 8 |
| **7k** | 4.84 | 53.9 | 64 |
| **8k** | 5.47 | 76.6 | 26 |

As shown for another secondary (**k**) and a branched halide (**j**), the formation of *N*3-alkylated products was also much faster than *O*-alkylation. NMR data in Table 2 further attest to the necessity of using $^{13}$C chemical shifts compared with the corresponding $^1$H resonances. Given these results, it is highly likely that the number of *O*-alkylated products reported in the literature without any corroborating $^{13}$C NMR data is artificially high on account they are either wrongly assigned or dubious.[2a,2c,2d,3a,3b] By way of example, a structure reported as 4-phenoxybutoxyquinazoline[2b] is, in fact, 3-phenoxybutyl-3,4-dihydroquinazoline-4-one based on $^{13}$C NMR data.

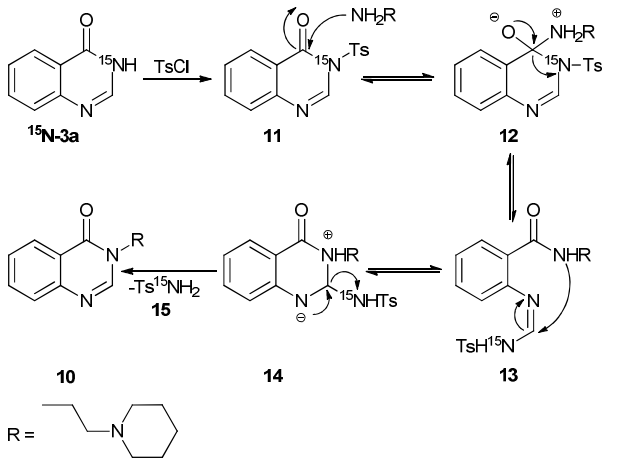
Returning to our initial goal of synthesizing 4-alkoxyquinazolines in a reliable manner, we found that attempted cyclization of *N*-formyl *o*-aminobenzonitriles via nucleophilic attack of the nitrile group by alkoxides[10a] resulted in preferential deprotection of the formyl moiety.

Conversion of quinazolinone **3a** into the corresponding tosylate with subsequent attack by alkoxide led to an inseparable mixture of products. Interestingly, when the tosylate was prepared *in situ* and treated with amine **9**, the only product obtained in 72% yield was compound **10** (Scheme 5). While a similar process was described in the literature as early as 1962,[10b] no mechanism was proposed.




**Scheme 5.** Reaction of quinazolinone **3a** with TsCl/amine

Hence, an experiment with $^{15}$N-labeled quinazolinone **3a**[10c] was carried out resulting in the isolation of unlabeled **10** and $^{15}$N-labeled *p*-toluenesulfonamide[10d] (Scheme 6). The formation of both compounds is consistent with initial conversion of **3a** into *N*3-tosyl amide **11**, the carbonyl group of which is subsequently attacked by the amine. Subsequent cleavage of the C–N bond gives rise to imino compound **13**, which undergoes recyclization with concomitant expulsion of *p*-toluenesulfonamide **15**. Importantly, this mechanism agrees with that recently proposed for the preparation of *N*-alkylated quinazolinones by the reaction of **3a** with amines in the presence of HATU/DBU,[8a] the Mukaiyama reagent/DIPEA[8b] or the treatment of 3-(2-cyanophenyl)-3,4-dihydroquinazoline-4-one with amines.[11]




**Scheme 6.** Mechanism of the formation of **10**

$^{15}$N NMR spectra of $^{15}$N-quinazolinone **3a** and $^{15}$N-*p*-toluenesulfonamide **15** are shown in Fig. 3.

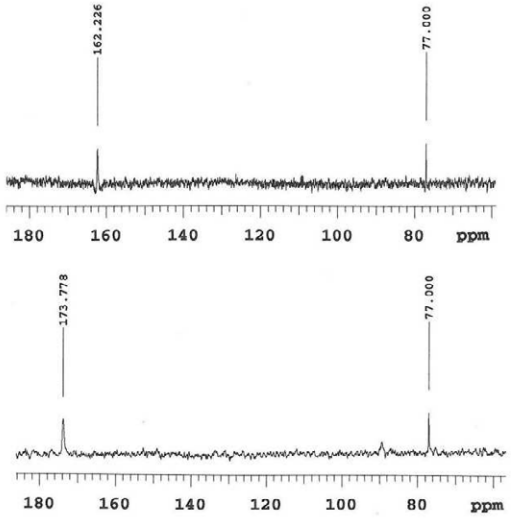
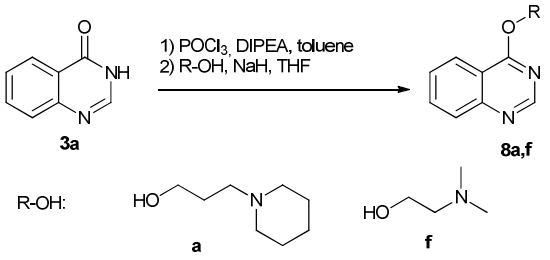



**Figure. 3** $^{15}$N NMR spectra of quinazolinone **3a** (top) and $^{15}$N-*p*-toluenesulfonamide (**15**) (bottom) with urea (77.00 ppm) as a standard.

An unambiguous route for the synthesis of 4-alkoxyquinazolines is demonstrated in Scheme 7 by employing the relatively unstable 4-chloroquinazoline,[12] and subsequent treatment with two alkoxides. This process afforded high yields of the corresponding 4-alkoxy compounds **8a** and **8f**.




**Scheme 7.** Preparation of *O*-alkylated quinazoline derivatives

**Table 3.** $^{1}$H- and $^{13}$C-NMR chemical shifts in $CD_3OD$ of C(1') group and the yields of compounds **8a** and **8f**

| Compound: | δH (ppm) | δC (ppm) | Isolated yield (%) |
|---|---|---|---|
| **8a** | 4.59 | 66.9 | 81 |
| **8f** | 4.78 | 65.5 | 82 |

**Computational Chemistry.** The trend shown by DFT calculations at the B3LYP/6-311+G(d,p) level of theory (Gaussian 03W) for selected representatives with a primary or secondary alkyl substituent (**7b** and **7i)** is consistent with experimental results. The *N3*-methylated product **7b** and *N3*-isopropyl derivative **7i** were found to have lower potential energies than their corresponding *O*-alkyl isomers. In a model reaction of compound **3a** with methyl bromide in the gas phase at 25 °C, activation energies of the transition states leading to all possible products (*N1*-, *N3*- and *O*-alkylation) determined from calculated free energies at 298 K were also in favor of the formation of **7b** ($E_a$= 9.34989 kcal/mol compared to $E_a$= 13.34273 kcal/mol for *N1*-methylation and and $E_a$= 11.53425 kcal/mol for *O*-methylation). For *i*-PrBr, however, the activation energies were slightly in favor of the *O*-isopropyl compound **8i** ($E_a$= 15.10666 kcal/mol compared to $E_a$= 16.98731 kcal/mol for *N3*-alkylation and $E_a$= 22.55206 kcal/mol for *N1*-alkylation).

## Conclusions

In conclusion, we have shown that alkylations of 2-unsubstituted 3,4-dihydroquinazoline-4-one proceed with exclusive or preferential formation of *N*3-alkylated products. While the use of primary halides leads exclusively to *N*3-alkylation, secondary or branched halides furnish minor amounts of *O*-alkylated compounds. Even though the reaction is trivial, using only $^{1}$H NMR data to assign the structure can be misleading and may result in incorrect structures being reported which are replicated throughout the literature. The $^{13}$C chemical shift of the alkylated carbon in the range of 45-55 ppm is a much more reliable indicator of *N*3-alkylation. Reporting correct structures is of particular importance in medicinal chemistry, since even very closely related structures often display diverse biological effects. Incorrect assignment of structures such as 4-phenoxybutoxyquinazoline and complete loss of biological activity (compared to *O*-alkylated heterocycles included in the study) constitutes an illustrative example.[2b]

4-Alkoxyquinazolines can be unambiguously prepared via the conversion of 3,4-dihydroquinazoline-4-ones into the corresponding 4-chloroquinazolines followed by $S_N$ reaction with alkoxides. Finally, $^{15}$N labeling brought solid evidence that tosylation of 3,4-dihydroquinazoline-4-one gives rise to the *N*3-tosylated product, which furnishes *N*3-alkyl-3,4-dihydroquinazoline-4-ones upon treatment with amines via

temporary opening of the quinazolinone ring and expulsion of the original N3 as a leaving group. This procedure **constitutes a more simple alternative to the recently reported protocols** based on the reaction of 3,4-dihydroquinazoline-4-one with amines in the presence of HATU/DBU[8a] or Mukaiyama's reagent/DIPEA.[8b]

**Experimental section**

General experimental procedure for the preparation of compounds **7a-h**: A mixture of 3,4-dihydroquinazolin-4-one (0.5 mmol), sodium iodide (0.05 mmol), potassium carbonate (2.5 mmol) and an appropriate alkylating agent (0.5 mmol) in acetone (5 mL) was heated under reflux for 24 hrs. The resultant mixture was diluted with ethyl acetate (10 mL), washed with brine (10 mL) and organic phase was dried with sodium sulfate. Crude products were purified by column chromatography (hexane – ethyl acetate 8:2).

3-[3-(Piperidin-1-yl)propyl]-3,4-dihydroquinazoline-4-one (**7a**). Yield: 83 %; white crystals, mp. 64-66 °C (lit.[13] no mp. mentioned); **$^1$H NMR:** (300 MHz, $CD_3OD$) δ 8.35 (1H, s, H2), 8.23-8.18 (1H, m, Ar), 7.83-7.77 (1H, m, Ar), 7.68-7.63 (1H, m, Ar), 7.56-7.50 (1H, m, Ar), 4.06 (2H, t, *J*=7.0 Hz, $CH_2$), 2.44-2.35 (6H, m, 3x$NCH_2$), 2.03-1.96 (2H, m, $CH_2$), 1.58-1.38 (6H, m, 3x$CH_2$); **$^{13}$C NMR:** (75 MHz, $CD_3OD$) δ 162.7, 149.4, 149.1, 135.6, 128.5, 127.8, 127.4, 123.0, 56.9, 55.3, 46.6, 26.5, 26.5, 25.2; **IR:** 1118, 1160, 1180, 1230, 1251, 1273, 1345, 1367, 1413, 1439, 1468, 1562, 1609, 1667, 2758, 2786, 2810, 2928, 2948 $cm^{-1}$; **LRMS (APCI):** *m/z* (relative intensity) 272.2 $[M+H]^+$ (100), 248.4 (1), 219.3 (1), 187.3 (14), 149.8 (1), 126.3 (1), 98.3 (1).

3-Methyl-3,4-dihydroquinazoline-4-one (**7b**). Yield: 95 %; white crystals, mp. 100-103 °C (lit.[11] 103-105 °C); **$^1$H NMR:** (300 MHz, $CD_3OD$) δ 8.25 (1H, s, H2), 8.23-8.19 (1H, m, Ar), 7.80-7.75 (1H, m, Ar), 7.65-7.61 (1H, m, Ar), 7.54-7.49 (1H, m, Ar), 3.58 (3H, s, $CH_3$); **$^{13}$C NMR:** (75 MHz, $CD_3OD$) δ 163.2, 149.5, 149.2, 135.6, 128.5, 127.8, 127.2, 122.8, 34.5; **IR:** 1106, 1152, 1187, 1264, 1295, 1321, 1339, 1397, 1469, 1561, 1609, 1665, 1863, 2924 $cm^{-1}$; **LRMS (APCI):** *m/z* (relative intensity) 161.2 $[M+H]^+$ (100), 147.2 (2), 134.3 (10), 129.0 (2), 116.3 (1), 102.3 (1), 86.1 (1).

3-Propyl-3,4-dihydroquinazoline-4-one (**7c**). Yield: 89 %; white crystals, mp. 84-85 °C (lit.[11] 82-84 °C); **$^1$H NMR:** (300 MHz, $CD_3OD$) δ 8.27 (1H, s, H2), 8.18 (1H, dd, $J_1$=8.1 Hz, $J_2$=1.6 Hz, Ar), 7.77 (1H, td, $J_1$=7.6 Hz, $J_2$=1.6 Hz, Ar), 7.63 (1H, dd, $J_1$=8.1 Hz, $J_2$=1.0 Hz, Ar), 7.50 (1H, td, $J_1$=7.6 Hz, $J_2$=1.0 Hz, Ar), 3.98 (2H, t, *J*=7.2 Hz, $NCH_2$), 1.82-1.75 (2H, m, $CH_2$), 0.96 (3H, t, *J*=7.5 Hz, $CH_3$); **$^{13}$C NMR:** (75 MHz, $CD_3OD$) δ 162.5, 149.1, 149.1, 135.6, 128.4, 127.8, 127.3, 122.9, 49.6, 23.5, 11.3; **IR:** 1025, 1093, 1108, 1152, 1179, 1242, 1259, 1292, 1326, 1368, 1377, 1474, 1564, 1610, 1667, 2879, 2938, 2968, 3070 $cm^{-1}$; **LRMS (APCI):** *m/z* (relative intensity) 189.3 $[M+H]^+$ (100), 170.9 (4), 147.3 (9), 87.3 (2), 75.2 (6).

3-Benzyl-3,4-dihydroquinazoline-4-one (**7d**). Yield: 91 %; white crystals, mp. 118-120 °C (lit.[14] 117-119 °C); **$^1$H NMR:** (300 MHz, $CD_3OD$) δ 8.39 (1H, s, H2), 8.21 (1H, dd, $J_1$=7.5 Hz, $J_2$=1.5 Hz, Ar), 7.78 (1H, td, $J_1$=7.0 Hz, $J_2$=1.4 Hz, Ar), 7.76 (1H, dd, $J_1$=6.5 Hz, $J_2$=0.9 Hz, Ar), 7.53 (1H, td, $J_1$=7.3 Hz, $J_2$=1.2 Hz, Ar), 7.39-7.23 (5H, m, Ar), 5.23 (2H, s, $CH_2$); **$^{13}$C NMR:** (75 MHz, $CD_3OD$) δ 162.5, 149.1, 149.0, 137.7, 135.8, 129.9, 129.1, 128.9, 128.7, 128.0, 127.5, 123.1, 50.7; **IR:** 1078, 1107, 1138, 1150, 1163, 1177, 1259, 1291, 1322, 1336, 1366, 1412, 1496, 1561, 1605, 1672, 2945, 3037, 3065 $cm^{-1}$; **LRMS (APCI):** *m/z* (relative intensity) 237.2 $[M+H]^+$ (12), 91.2 (100), 65.2 (2).

(4-Oxo-3,4-dihydroquinazolin-3-yl)acetate (**7e**). Yield: 90 %; white crystals, mp. 240-243 °C (lit.[15] 243-245 °C); **$^1$H NMR:** (500 MHz, $CD_3OD$) δ 8.28 (1H, s, H2), 8.22 (1H, dd, $J_1$=7.5 Hz, $J_2$=1.5 Hz, Ar), 7.84 (1H, td, $J_1$=7.0 Hz, $J_2$=1.5 Hz, Ar), 7.70 (1H, dd, $J_1$=7.5 Hz, $J_2$=1.0 Hz, Ar), 7.56 (1H, td, $J_1$=7.0 Hz, $J_2$=1.1 Hz, Ar), 4.81 (2H, s, $CH_2$); **$^{13}$C NMR:** (125 MHz, $CD_3OD$) δ; 170.9, 162.6, 149.3, 149.2, 136.0, 128.7, 128.0, 127.5, 122.8, 48.4; **IR:** 1109, 1175, 1208, 1299, 1377, 1482, 1612, 1666, 1688, 2921 $cm^{-1}$; **LRMS (APCI):** *m/z* (relative intensity) 205.3 $[M+H]^+$ (100), 189.3 (38), 173.3 (25), 158.5 (4), 147.1 (5), 129.1 (4), 102.3 (6), 72.1 (7).

3-(Dimethylamino)ethyl-3,4-dihydroquinazoline-4-one (**7f**). Yield: 90 %; white amorphous solid (lit.[16] mentioned oil); **$^1$H NMR:** (500 MHz, $CD_3OD$) δ 8.27 (1H, s, H2), 8.21 (1H, dd, $J_1$=7.2 Hz, $J_2$=1.4 Hz, Ar), 7.78 (1H, td, $J_1$=7.0 Hz, $J_2$=1.4 Hz, Ar), 7.73 (1H, dd, $J_1$=7.5 Hz, $J_2$=1.0 Hz, Ar), 7.52 (1H, td, $J_1$=7.0 Hz, $J_2$=1.0 Hz, Ar), 4.18 (2H, t, *J*=6.3 Hz, $CH_2$), 2.72 (2H, t, *J*=6.3 Hz, $CH_2$), 2.31 (6H, s, 2x$CH_3$); **$^{13}$C NMR:** (125 MHz, $CD_3OD$) δ 162.7, 149.3, 149.1, 135.7, 128.5, 127.8, 127.4, 123.0, 58.5, 45.6, 45.2**; IR:** 1034, 1134, 1149, 1181, 1292, 1322, 1367, 1473, 1608, 1667, 2770, 2822, 2945 $cm^{-1}$ ; **LRMS (APCI):** *m/z* (relative intensity): 218.2 $[M+H]^+$ (100), 204.3 (28), 173.1 (49), 154.5 (1), 129.1 (4), 103.1 (1), 72.1 (3).

3-[2-(Pyrrolidin-1-yl)ethyl]-3,4-dihydroquinazoline-4-one (**7g**). Yield: 96 %; yellowish crystals, mp. 148-150 °C (lit.[17] 150 °C); **$^1$H NMR:** (300 MHz, $CD_3OD$) δ 8.26 (1H, s, H2), 8.18-8.14 (1H, m, Ar), 7.77-7.72 (1H, m, Ar), 7.63-7.59 (1H, m, Ar), 7.50-7.44 (1H, m, Ar), 4.16 (2H, t, *J*=6.7 Hz, $OCH_2$), 2.85 (2H, t, *J*=6.7 Hz, $NCH_2$), 2.66-2.58 (4H, m, 2x$CH_2$), 1.80-1.72 (4H, m, 2x$CH_2$); **$^{13}$C NMR:** (75 MHz, $CD_3OD$) δ 162.4, 149.1, 148.9, 135.5, 128.3, 127.8, 127.3, 122.9, 55.3, 55.1, 46.3, 24.3; **IR:** 1105, 1118, 1148, 1175, 1295, 1325, 1369, 1450, 1472, 1605, 1671, 2696, 2782, 2920 $cm^{-1}$; **LRMS (APCI):** *m/z* (relative intensity) 244.2 $[M+H]^+$ (100), 203.3 (1), 187.2 (1), 173.2 (5), 158.2 (1), 126.1 (1), 112.3 (1), 98.1 (3).

3-[2-(1-Methylpyrrolidin-2-yl)ethyl]-3,4-dihydroquinazoline-4-one (**7h**). Yield: 89 %; yellowish amorphous solid; **$^1$H NMR:** (300 MHz, $CD_3OD$) δ 8.33 (1H, s, H2), 8.17-8.13 (1H, m, Ar), 7.79-7.73 (1H, m, Ar), 7.63-7.59 (1H, m, Ar), 7.53-7.46 (1H, m, Ar), 4.10-4.02 (2H, t, *J*=7.7 Hz, $OCH_2$), 3.08-3.00 (1H, m, CH), 2.38-2.02 (7H, m, 2x$CH_2$+$CH_3$), 1.82-1.53 (4H, m, 2x$CH_2$); **$^{13}$C NMR:** (75 MHz, $CD_3OD$) δ 162.4, 149.0, 135.6, 128.4, 127.9, 127.3, 122.9, 65.3, 57.7, 45.7, 40.5, 33.6, 31.2, 22.7; **IR:** 1106, 1164, 1180, 1292, 1323, 1371, 1473, 1563, 1609, 1669, 2784, 2947, 3414 $cm^{-1}$; **LRMS (APCI):** *m/z* (relative intensity) 258.3 $[M+H]^+$ (100), 217.2 (4), 203.3 (2), 175.2 (1), 147.4 (4), 128.2 (3), 112.2 (6), 81.0 (2); Anal. Calcd for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 70.11; H, 7.28; N, 16.24.

General experimental procedure for method A: A mixture of 3,4-dihydroquinazoline-4-one (0.5 mmol), sodium hydride (1.0 mmol) and an appropriate alkylating agent (0.5 mmol) in dry DMF (3 mL) was heated at 90 °C under Ar for 12 hrs. The resultant mixture was diluted with ethyl acetate (10 mL), washed with brine (10 mL) and dried over sodium sulfate. The product was purified by column chromatography (hexane – ethyl acetate 8:2).

General experimental procedure for method B: A mixture of 3,4-dihydroquinazoline-4-one (0.5 mmol), a catalytic amount of tetrabutylammonium iodide and an appropriate alkylating agent (0.5 mmol) in 1M NaOH (2 mL) and dichloromethane (2 mL) was vigorously stirred at rt for 48 hrs. The organic phase was dried over sodium sulfate, and the crude product purified by column chromatography (hexane – ethyl acetate 8:2).

General experimental procedure for method C: A mixture of 3,4-dihydroquinazoline-4-one (0.5 mmol), potassium carbonate (1.0 mmol) and an appropriate alkylating agent (0.5 mmol) in DMF (3 mL) was stirred at rt for 48 hrs. The resultant mixture was diluted with ethyl acetate (10 mL), washed with brine (10

mL) and dried over sodium sulfate. The product was purified by column chromatography (hexane – ethyl acetate 8:2).

General experimental procedure for method D: A mixture of 3,4-dihydroquinazoline-4-one (0.5 mmol), sodium hydroxide (1.0 mmol) and an appropriate alkylating agent (0.5 mmol) in water (3 mL) was heated at 90 °C for 24 hrs. Ethyl acetate (10 mL) was then added, the layers were separated and the organic phase dried over sodium sulfate. The product was purified by column chromatography (hexane – ethyl acetate 8:2).

General experimental procedure for the preparation of compounds **7i-8j**: A mixture of 3,4-dihydroquinazolin-4-one (0.5 mmol), sodium iodide (0.05 mmol), potassium carbonate (2.5 mmol) and an appropriate alkylating agent (0.5 mmol) in DMF (5 mL) was heated at 100 °C for 24 hrs. The resultant mixture was diluted with ethyl acetate (10 mL), washed with brine (10 mL) and dried over sodium sulfate. The products were purified by column chromatography (hexane – ethyl acetate 8:2).

3-Isopropyl-3,4-dihydroquinazoline-4-one (**7i**). Yield: 66 %; white crystals, mp. 87-89 °C (lit.[18] 87-88 °C); **$^1$H NMR:** (300 MHz, $CD_3OD$) δ 8.34 (1H, s, H2), 8.18 (1H, dd, *J*=8.1, 1.6 Hz, Ar), 7.77 (1H, td, *J*=7.7, 1.6 Hz, Ar), 7.63 (1H, d, *J*=8.1 Hz, Ar), 7.50 (1H, td, *J*=7.6, 1.2 Hz, Ar), 5.07 (1H, sep, *J*=6.9 Hz, CH), 1.49 (6H, d, *J*=6.9 Hz, 2x$CH_3$); **$^{13}$C NMR:** (75 MHz, $CD_3OD$) δ 162.1, 148.5, 146.2, 135.5, 128.4, 127.7, 127.5, 122.8, 48.4, 21.7; **IR:** 1082, 1103, 1147, 1182, 1247, 1266, 1330, 1370, 1400, 1464, 1475, 1564, 1604, 1660, 2931, 2981, 3048 cm$^{-1}$; **LRMS (APCI):** *m/z* (relative intensity) 189.3 $[M+H]^+$ (100), 170.6 (17), 147.3 (23).

4-Isopropyloxyquinazoline (**8i**). Yield: 18 %; colorless amorphous solid, (lit.[6] no mp. mentioned); **$^1$H NMR:** (500 MHz, $CD_3OD$) δ 8.70 (1H, s, H2), 8.16 (1H, d, *J*=8.5 Hz, Ar), 7.89 (1H, td, *J*=7.5, 1.5 Hz, Ar), 7.84 (1H, d, *J*=8.0 Hz, Ar), 7.62 (1H, td, *J*=7.5, 1.4 Hz, Ar), 5.65 (1H, sep, *J*=6.2 Hz, CH), 1.47 (6H, d, *J*=6.2 Hz, 2x$CH_3$); **$^{13}$C NMR:** (125 MHz, $CD_3OD$) δ 167.9, 155.6, 151.5, 135.2, 128.6, 127.6, 124.7, 118.0, 72.1, 22.0; **IR:** 1086, 1105, 1159, 1188, 1297, 1324, 1384, 1413, 1494, 1572, 1619, 2938, 2981, 3046 cm$^{-1}$; **LRMS (APCI):** *m/z* (relative intensity) 189.2 $[M+H]^+$ (100), 170.9 (89), 147.2 (36).

3-Isobutyl-3,4-dihydroquinazoline-4-one (**7j**). Yield: 75 %; yellowish amorphous solid; **$^1$H NMR:** (300 MHz, $CD_3OD$) δ 8.25 (1H, s, H2), 8.19 (1H, d, *J*=7.5 Hz, Ar), 7.78 (1H, t, *J*=7.5 Hz, Ar), 7.65 (1H, d, *J*=8.2 Hz, Ar), 7.51 (1H, t, *J*=7.8 Hz, Ar), 3.83 (2H, d, *J*=7.4 Hz, $CH_2$), 2.26-2.06 (1H, m, CH), 0.94 (6H, d, *J*=6.8 Hz, 2x$CH_3$); **$^{13}$C NMR:** (75 MHz, $CD_3OD$) δ 162.7, 149.4, 149.0, 135.6, 128.5, 127.9, 127.4, 122.9, 54.9, 29.2, 20.0; **IR:** 1026, 1109, 1146, 1177, 1238, 1260, 1291, 1323, 1377, 1474, 1564, 1610, 1673, 2872, 2935, 2961 cm$^{-1}$; **LRMS (APCI):** *m/z* (relative intensity) 203.4 $[M+H]^+$ (100), 170.5 (2), 147.4 (8); Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.35; H, 7.07; N, 13.91.

4-Isobutyloxyquinazoline (**8j**). Yield: 8 %; yellowish amorphous solid; **$^1$H NMR:** (500 MHz, $CD_3OD$) δ 8.71 (1H, s, H2), 8.22 (1H, d, *J*=8.0 Hz, Ar), 7.92 (1H, t, *J*=7.5 Hz, Ar), 7.88 (1H, d, *J*=8.5 Hz, Ar), 7.66 (1H, t, *J*=7.6 Hz, Ar), 4.41 (2H, d, *J*=6.5 Hz, $CH_2$), 2.30-2.18 (1H, m, CH), 1.10 (6H, d, *J*=6.8 Hz, 2x$CH_3$); **$^{13}$C NMR:** (125 MHz, $CD_3OD$) δ 168.6, 155.6, 151.5, 135.3, 128.8, 127.7, 124.6, 117.8, 74.6, 29.1, 19.5; **IR:** 1093, 1159, 1188, 1294, 1359, 1386, 1421, 1470, 1496, 1573, 1620, 2854, 2873, 2927, 2960 cm$^{-1}$; **LRMS (APCI):** *m/z* (relative intensity) 203.4 $[M+H]^+$ (100), 171.0 (19), 147.4 (81), 87.3 (8), 73.3(7); Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.41; H, 7.12; N, 13.61.

3-(Butan-2-yl)-3,4-dihydroquinazoline-4-one (**7k**). Yield: 64 %; white crystals, mp. 71-72 °C (lit.[19] no details mentioned); **$^1$H NMR:** (300 MHz, $CD_3OD$) δ 8.28 (1H, s, Ar), 8.17 (1H, dd, *J*=8.2, 1.3 Hz, Ar), 7.75 (1H, ddd, *J*=8.5, 7.4, 1.8 Hz, Ar), 7.63 (1H, d, *J*=7.8 Hz, Ar), 7.48 (1H, ddd, *J*=8.0, 7.2, 1.2 Hz, Ar), 4.90 – 4.78 (1H, m, CH), 1.95 – 1.75 (2H, m, $CH_2$), 1.45 (3H, d, *J*=6.9 Hz, $CH_3$), 0.84 (3H, t, *J*=7.5 Hz, $CH_3$); **$^{13}$C NMR:** (75 MHz, $CD_3OD$) δ 162.3, 148.4, 146.4, 135.5, 128.4, 127.7, 127.6, 122.7, 53.9, 29.5, 20.0, 11.1; **IR:** 1090, 1147, 1177, 1247, 1291, 1328, 1397, 1474, 1564, 1603, 1659, 2853, 2873, 2927, 2973 cm$^{-1}$; **LRMS (APCI):** *m/z* (relative intensity) 203.6 $[M+H]^+$ (100), 147.6 (63), 87.6 (2), 73.6 (2).

4-(Butan-2-yloxy)quinazoline (**8k**). Yield: 26 %; yellowish amorphous solid; **$^1$H NMR:** (300 MHz, $CD_3OD$) δ 8.68 (1H, s, Ar), 8.13 (1H, d, *J*=8.2 Hz, Ar), 7.90 – 7.79 (2H, m, Ar), 7.58 (1H, ddd, *J*=8.1, 6.2, 1.9 Hz, Ar), 5.53-5.41 (1H, m, CH), 1.93 – 1.68 (2H, m, $CH_2$), 1.40 (3H, d, *J*=6.4 Hz, $CH_3$), 0.99 (3H, t, *J*=7.4 Hz, $CH_3$); **$^{13}$C NMR:** (75 MHz, $CD_3OD$) δ 168.2, 155.6, 151.5, 135.2, 128.5, 127.6, 124.6, 118.0, 76.6, 29.8, 19.5, 10.0; **IR:** 1088, 1158, 1187, 1292, 1334, 1377, 1414, 1493, 1572, 1619, 2852, 2872, 2927, 2972 cm$^{-1}$; **LRMS (APCI):** *m/z* (relative intensity) 203.7 $[M+H]^+$ (20), 147.7 (100), 87.7 (8), 73.7 (10); Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.98; H, 6.89; N, 13.84.

3-[2-(Piperidin-1-yl)ethyl]-3,4-dihydroquinazoline-4-one (**10**). Tosyl chloride (0.6 mmol) was added in three portions to a cooled suspension (0 °C) of 3,4-dihydroquinazoline-4-one (0.5 mmol), triethylamine (0.6 mmol) and a catalytic amount of DMAP in dry dichloromethane (5 mL). After 10 mins of stirring, the reaction mixture was allowed to warm to rt, 2-(piperidin-1-yl)ethylamine (0.5 mmol) was added, and the resultant mixture was heated under reflux for 24 hrs. The mixture was diluted with ethyl acetate (10 mL), washed with brine (10 mL) and dried over sodium sulfate. The product was purified by column chromatography (ethyl acetate).Yield: 72 %; yellowish crystals, mp. 74-76 °C (lit.[20] no mp. mentioned); **$^1$H NMR:** (300 MHz, $CD_3OD$) δ 8.27 (1H, s, H2), 8.22 (1H, dd, *J*=8.5, 1.5 Hz, H5), 7.81 (1H, td, *J*=7.5, 1.7 Hz, H7), 7.67 (1H, d, *J*=8.0 Hz, H8), 7.54 (1H, td, *J*=7.5, 1.2 Hz, H6), 4.16 (2H, t, *J*=6.5 Hz, H1'), 2.68 (2H, t, *J*=6.5 Hz, H2'), 2.55-2.45 (4H, m, 2x$NCH_2$), 1.59-1.54 (4H, m, 2x$CH_2$), 1.47-1.42 (2H, m, $CH_2$); **$^{13}$C NMR:** (75 MHz, $CD_3OD$) δ 162.6, 149.6, 149.1, 135.7, 128.4, 127.8, 127.4, 123.0, 58.0, 55.6, 44.8, 26.8, 25.1; **IR:** 1110, 1153, 1172, 1263, 1303, 1322, 1364, 1382, 1443, 1466, 1473, 1608, 1664, 2782, 2827, 2850, 2938 cm$^{-1}$ **LRMS (APCI):** *m/z* (relative intensity) 258.3 $[M+H]^+$ (100), 246.9 (5), 225.3 (14), 199.0 (1), 183.1 (2), 173.1 (59), 162.1 (7), 112.1 (19), 97.9 (2), 82.2 (1).

General procedure for the preparation of compounds **8a** and **8f**. $POCl_3$ (2.4 mmol) was slowly added to a cooled (0 °C) suspension of 3,4-dihydroquinazolin-4-one (2.0 mmol) and diisopropylamine (2.6 mmol) in toluene (10 mL) and the resultant mixture was stirred at 90 °C for 3 hrs. The mixture was diluted with ethyl acetate (10 mL), washed with brine (10 mL) and dried over sodium sulfate. The product (4-chloroquinazoline) was purified by column chromatography (hexane - ethyl acetate 95:5).

Sodium (1.2 mmol) was added to a solution of an alcohol (1.0 mmol) in dry THF and the mixture was stirred at rt for 1 hr. 4-Chloroquinazoline (1.0 mmol) was then added, and the resultant solution was stirred at rt for 24 hrs. The mixture was diluted with ethyl acetate (10 mL), washed with brine (10 mL) and dried over sodium sulfate. The products were purified by column chromatography (hexane - ethyl acetate 9:1).

4-[3-(Piperidin-1-yl)propyloxy]quinazoline (**8a**). Yield: 81 %; yellowish amorphous solid; **$^1$H NMR:** (300 MHz, $CD_3OD$) δ 8.67 (1H, s, H2), 8.11 (1H, d, *J*=8.2 Hz, Ar), 7.90-7.79 (2H, m, Ar), 7.59 (1H, td, *J*=7.4, 1.7 Hz, Ar), 4.59 (2H, t, *J*=6.3 Hz, $CH_2$), 2.63 (2H, t, *J*=7.8 Hz, $CH_2$), 2.59-2.49 (4H, m, 2x$CH_2$), 2.17-2.06 (2H, m, $CH_2$), 1.67-1.54 (4H, m, 2x$CH_2$), 1.50-1.39 (2H, m, $CH_2$); **$^{13}$C NMR:** (75 MHz, $CD_3OD$) δ 168.1, 155.4, 151.4,

135.2, 128.7, 127.7, 124.5, 117.5, 66.9, 56.7, 55.3, 26.6, 26.2, 24.8; **IR:** 1099, 1121, 1157, 1298, 1352, 1421, 1530, 1573, 1621, 2856, 2937, 3062 $cm^{-1}$; **LRMS (APCI):** *m/z* (relative intensity) 272.3 $[M+H]^+$ (100), 253.8 (1), 222.2 (1), 187.2 (2), 170.6 (3), 146.6 (8), 126.3 (7); Anal. Calcd for $C_{16}H_{21}N_3O$: C, 70.82; H, 7.80; N, 15.49. Found: C, 70.96; H, 7.77; N, 15.53.

4-(Dimethylamino)ethyloxyquinazoline (**8f**). Yield: 82 %; yellowish amorphous solid (lit.[21] no mp. mentioned); **$^1$H NMR:** (300 MHz, $CD_3OD$) δ 8.74 (1H, s, H2), 8.28 (1H, d, *J*=8.3 Hz, Ar), 7.93 (1H, t, *J*=7.4 Hz, Ar), 7.88 (1H, d, *J*=8.5 Hz, Ar), 7.68-7.64 (1H, m, Ar), 4.78 (2H, t, *J*=5.4 Hz, $CH_2$), 3.02 (2H, t, *J*=5.4 Hz, $CH_2$), 2.47 (6H, s, 2x$CH_3$); **$^{13}$C NMR:** (75 MHz, $CD_3OD$) δ 168.2, 155.4, 151.6, 135.4, 128.8, 127.7, 124.9, 117.6, 65.5, 58.4, 45.6**; IR:** 1097, 1160, 1297, 1343, 1380, 1421, 1469, 1497, 1573, 1619, 1677, 2774, 2822, 2950, 3064 $cm^{-1}$ ; **LRMS (APCI):** *m/z* (relative intensity): 218.2 $[M+H]^+$ (100), 204.2 (31), 190.2 (8), 173.2 (17), 147.2 (19), 126.3 (4), 87.2 (2), 72.2 (34).

**Computational Chemistry**. Calculations were perfomed using Gaussian 03W, version 6.1, revision-E.01 (Gaussian, Inc.). Geometry of the ground states of the molecules was optimized using the B3LYP/6-311+G(d,p) level of theory. All energy optimized structures were checked by the vibrational analysis (no negative frequencies). Transition states (saddle point of order 1) were calculated using the Berny algorithm. The software GaussView, version 4.1.2 (Gaussian, Inc.) was used for visualisation of orbitals.

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