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Base dependent purported synthesis of congested 2-aminobenzylamines and tetrahydro-2-oxoquinazolines from 2-pyranones

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ABSTRACT

An expeditious and concise synthesis of highly congested 2-amino-3-aminomethyl-5-methylsulfanyl/-*sec*-aminobiphenyl-4-carbonitrile **4** and 1-*tert*-butoxycarbonyl-6-*sec*-amino-8-aryl-5-cyano-2-*oxo*-1,2,3,4-tetrahydroquinazoline **5** has been delineated through base catalyzed ring transformation of 6-aryl-4-methylsulfanyl/-*sec*-amino-2*H*-pyran-2-one-3-carbonitrile **1** with 1,3-bis(*tert*-butoxycarbonylamino)-2-propanone **2**, followed by TFA catalyzed hydrolysis of the intermediate [3-*tert*-butoxycarbonyl-aminomethyl-4-cyano-5-methylsulfanyl/-*sec*-aminobiphenyl-2-yl]carbamic acid *tert*-butyl ester **3** in moderate yield. The mechanism of formation of **5** has been established through isolation and transformation of the intermediate **3** to the 1-*tert*-butoxycarbonyl-6-*sec*-amino-8-aryl-5-cyano-2-*oxo*-1,2,3,4-tetrahydroquinazoline.

1. Introduction

Quinazolines and 2-aminobenzylamines are of great importance in synthetic and medicinal chemistry.[1] Quinazolines (**I**–**IV**)[2,3] and benzodiazepines (**V**)[4] are usually synthesized from 2-amino-benzylamines, which are also useful intermediate for the construction of hardening agents for resins,[5] Figure 1. A literature search on quinazoline nucleus revealed that chemistry of 2,3-dihydro-4(1*H*)-quinazolinone **III** have been explored extensively while that of 3,4-dihydro-2(1*H*)-quinazolinone **IV** ring system is underdeveloped.

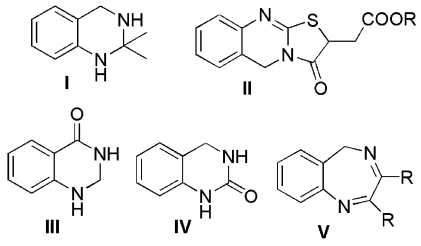

Figure 1. Pharmacologically active quinazoline frameworks.

3,4-Dihydro-2(1*H*)-quinazolinone **IV** is considered as a fused bicyclic urea derivative, which plays a significant role in organic, medicinal, supramolecular, and material chemistry.[6] Recently, cyclic and acyclic ureas are reported[7] as potent HIV-1 protease inhibitors, *P38* MAP kinase inhibitors for the management of inflammatory diseases,[8] in addition to anticonvulsant and antihypertensive activities.[9,10]

2-Aminobenzylamines are usually prepared[11] by the reaction of 2-nitrobenzyl chloride, 2-nitrobenzaldehyde, 2-aminobenzophenone, 2-aminoactophenones, 2-aminopropiophenones with ammonia followed by reduction.[12,13] Other approaches include lithium borohydride reduction[14] of 2-aminobenzamide and hydrogenation of 2-aminobenzaldehyde oxime or 2-nitrobenzalamine over Raney nickel in ethanol followed by refluxing with Zn dust, ammonium acetate, and aqueous ammonia in ethanol.[8,15]

The reaction of amines with isocyanates is a very common approach for the construction of cyclic ureas.[16] Alternative approaches are the use of dialkyl carbonates,[17] diimidazol-1-yl-methane,[18,19] *S*,*S*-dimethyldithiocarbonate (DMTDC),[20] and carbon monoxide in the presence of selenium[21] for carbonylation of amines for the construction of 3,4-dihydro-2(1*H*)-quinazolinones. Oxidative carbonylation of primary amines to cyclic ureas in the presence of $W(CO)_6/I_2$ has been proved to be a useful approach for the synthesis of 3,4-dihydro-2(1*H*)-quinazolinones.[22] The synthetic limitations of earlier procedures in terms of use of expensive reagents and catalysts, exposure to corrosive and toxic chemicals, requirement of high temperature and pressure, and compatibility of reagents to the functional groups present necessitated to develop an efficient and concise protocol for the construction of aryl-tethered 3,4-dihydro-2(1*H*)

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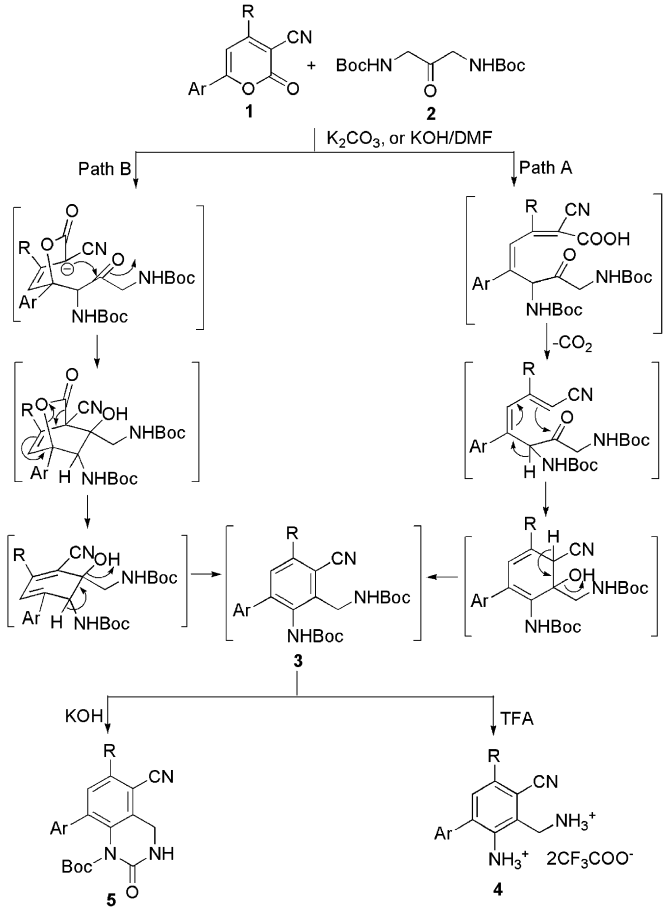
quinazolinones. Herein, we report a practical synthesis of highly congested aryl-tethered 2-aminobenzylamines **3**, **4** and aryl-tethered 3,4-dihydro-2(1*H*)quinazolinones **5** through base catalyzed ring transformation of 6-aryl-4-*sec*-amino-2*H*-pyran-2-one-3-carbonitriles **1** by 1,3-bis(*tert*-butoxycarbonylamino)-2-propanone **2**.

2. Results and discussion

The desired 1,3-bis(*tert*-butoxycarbonylamino)-2-propanone **2** was obtained[23] from the reaction of 1,3-diaminopropan-2-ol and di-*tert*-butyl dicarbonate followed by Swern oxidation. The various 6-aryl-4-*sec*-amino-2*H*-pyran-2-one-3-carbonitriles **1** used as a precursor were prepared from the reaction of methyl 2-cyano-3,3-dimethylthioacrylate[24] and aryl methyl ketone followed by amination[25] with secondary amines in boiling ethanol.

It is evident from the topography of 6-aryl-4-*sec*-amino-2*H*-pyran-2-one-3-carbonitriles that they possess three electrophilic centers C-2, C-4, and C-6 in which latter is highly prone to nucleophilic attack due to extended conjugation and the presence of an electron-withdrawing CN substituent at position 3 of the pyran ring. There are two probable paths **A** and **B** for this ring transformation reaction. The initial step in path **B** is the formation of Michael adduct through attack of carbanion generated in situ from 1,3-bis(*tert*-butoxycarbonylamino)-2-propanone **2** at most electron deficient center C-6 of the lactone **1** followed by ring closure with the loss of water and carbon dioxide to provide ring transformed product **3**. The alternate path **A** for this reaction is attack of carbanion from **2** at C-6 of **1** with ring opening followed by intramolecular cyclization involving C-3 of the pyran ring with loss of carbon dioxide and water to form **3** as depicted in Scheme 1. The Diels–Alder mechanism for this reaction is ruled out as this reaction is carried out at room temperature under very mild condition, which is inappropriate[26] for this substrate under applied experimental conditions.



Scheme 1. Plausible mechanisms for the formation of **3**, **4**, and **5**.

Table 1
A list of the synthesized compounds **3**, **4**, and **5**

3,4,5	Ar	R	Yield (%)
3a	4-BrC_6H_4	SCH_3	62
3b	4-BocNHC_6H_4	SCH_3	55
3c	4-MeOC_6H_4	SCH_3	64
3d	2-Naphthyl	SCH_3	57
3e	2-Naphthyl	Piperidin-1-yl	59
3f	2-Naphthyl	4-Methylpiperidin-1-yl	61
3g	2-Naphthyl	Morpholin-4-yl	58
3h	2-Naphthyl	4-Phenylpiperazin-1-yl	56
3i	4-BrC_6H_4	4-Phenylpiperazin-1-yl	53
3j	2-Naphthyl	Dimethylamino	60
4a	4-BrC_6H_4	SCH_3	95
4b	4-MeOC_6H_4	SCH_3	96
4c	2-Naphthyl	4-Phenylpiperazin-1-yl	97
5a	2-Naphthyl	Dimethylamino	72
5b	2-Naphthyl	Piperidin-1-yl	74
5c	2-Naphthyl	4-Phenylpiperazin-1-yl	68
5d	2-Naphthyl	Morpholin-4-yl	70
5e	4-BrC_6H_4	Pyrrolidin-1-yl	76

Thus, stirring a reaction mixture of 6-aryl-4-*sec*-amino-2*H*-pyran-2-one-3-carbonitriles **1** and 1,3-bis(*tert*-butoxycarbonylamino)-2-propanone **2** in the presence of K_2CO_3 in DMF gave 2-(*tert*-butoxycarbonylaminomethyl)-3-*tert*-butoxycarbonylamino-6-*sec*-amino-4-benzonitrile[27] **3**, which was subsequently hydrolyzed with TFA to give diamine **4** as the trifluoroacetate salt, Scheme 1. It was found that the use of KOH in lieu of K_2CO_3 produced a product different from **3** and was characterized as 1-*tert*-butoxycarbonyl-6-*sec*-amino-8-aryl-5-cyano-2-*oxo*-1,2,3,4-tetrahydroquinazoline **5** in moderate yields (Table 1). It is possible that formation of **5** takes place through in situ formation of **3** as intermediate, which in due course cyclizes to **5** as shown in Scheme 1. The formation of **3** as a key intermediate in the synthesis of **5** was confirmed by conversion of **3** to compound **5** on stirring in the presence of powdered KOH in DMF. It is expected that KOH promoted abstraction of proton from the Boc protected amino group, directly attached to the phenyl ring in the presence of the CN group at the *meta* position of **3** facilitates the cyclization to give 1-*tert*-butoxycarbonyl-6-*sec*-amino-8-aryl-5-cyano-2-*oxo*-1,2,3,4-tetrahydroquinazoline **5** (Table 1).

3. Conclusion

We have developed a facile, economical, and efficient route to the synthesis of highly congested 2-aminobenzylamine and tetrahydro-2-oxoquinazolines. The methodology also provides an opportunity to append diverse functionalities such as *sec*-amino, methylsulfanyl, cyano, and aryl groups into the molecular structure of the product.

4. Experimental

4.1. General

All reactions were conducted in flame dried glassware. Precoated Merck TLC plates were used for monitoring progress of the reactions. Column chromatographic separations were performed on silica gel (60–120 mesh). IR spectra were recorded on a Shimadzu 8201 PC FTIR spectrophotometer. ^{1}H NMR spectra were recorded on Brucker DRX 200 as well as Bruker DRX 300 spectrometers in deuterated solvents with TMS as internal reference. Mass spectra were recorded on JEOL SX-102 (FAB) spectrometer. Melting points were determined on Büchi-530 capillary melting point apparatus and are uncorrected. Elemental analyses were performed on a Carlo Erba 108 or an Elementar Vario EL III microanalyzer at CDRI, Lucknow 226001, India.

4.2. General procedure for the synthesis of [3-(*tert*-butoxycarbonylaminomethyl)-4-cyano-5-methylsulfanyl-biphenyl-2-yl]-carbamic acid *tert*-butyl ester (3a–d) and [6-aryl-2-(*tert*-butoxycarbonylaminomethyl)-3-cyano-4-*sec*-aminophenyl]-carbamic acid *tert*-butyl ester (3e–j)

A mixture of **1** (1.0 mmol) and **2** (288 mg, 1.0 mmol) was stirred for 4 h in a suspension of powdered K_2CO_3 (207 mg, 1.5 mmol) in DMF (5 mL). The progress of the reaction was monitored by TLC in a mixture of hexane–ethyl acetate (7:3). The reaction mixture was poured into ice cold water and neutralized with 10% HCl. The solid precipitate obtained was filtered, washed with water, and purified on silica gel chromatography by eluting with hexane–ethyl acetate (9:1).

*4.2.1. [4′-Bromo-3-(tert-butoxycarbonylaminomethyl)-4-cyano-5-methylsulfanyl-biphenyl-2-yl]-carbamic acid tert-butyl ester (**3a**)*

White amorphous solid; mp 182–183 °C. [Found: C, 54.66; H, 5.56; N, 7.59. $C_{25}H_{30}BrN_3O_4S$ requires: C, 54.74; H, 5.51; N, 7.66%.] ν_{max} (KBr) 3329, 2221, 1697 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.25 (9H, s, Boc), 1.44 (9H, s, Boc), 2.44 (3H, s, SCH_3), 4.70 (2H, s, CH_2), 5.53 (1H, br s, NH), 7.16 (1H, s, ArH), 7.28 (2H, d, *J* 7.8 Hz, ArH), 7.55 (2H, d, *J* 7.8 Hz, ArH), 8.19 (1H, br s, NH); MS (FAB): *m/z* 548 (MH^+).

*4.2.2. [2′-tert-Butoxycarbonylamino-3′-(tert-butoxycarbonyl-aminomethyl)-4′-cyano-5′-methylsulfanyl-biphenyl-4-yl]-carbamic acid tert-butyl ester (**3b**)*

White powder; mp 185–186 °C. [Found: C, 61.58; H, 6.82; N, 9.60. $C_{30}H_{40}N_4O_6S$ requires: C, 61.62; H, 6.90; N, 9.58%.] ν_{max} (KBr) 3334, 2220, 1725 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.46 (9H, s, Boc), 1.54 (9H, s, Boc), 1.56 (9H, s, Boc), 2.46 (3H, s, SCH_3), 4.72 (2H, s, CH_2), 5.01 (1H, br s, NH), 7.14 (1H, s, ArH), 7.30 (2H, d, *J* 8.4 Hz, ArH), 7.52 (2H, d, *J* 8.4 Hz, ArH), 8.19 (1H, br s, NH); MS (FAB): *m/z* 585 (MH^+).

*4.2.3. [3-(tert-Butoxycarbonylaminomethyl)-4-cyano-4′-methoxy-5-methylsulfanyl-biphenyl-2-yl]-carbamic acid tert-butyl ester (**3c**)*

White amorphous solid; mp 135–136 °C. [Found: C, 62.58; H, 6.80; N, 8.50. $C_{26}H_{33}N_3O_5S$ requires: C, 62.50; H, 6.66; N, 8.41%.] ν_{max} (KBr) 3338, 2219, 1716 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.46 (9H, s, Boc), 1.60 (9H, s, Boc), 2.47 (3H, s, SCH_3), 3.87 (3H, s, OCH_3), 4.76 (2H, s, CH_2), 5.90 (1H, br s, NH), 6.99 (1H, s, ArH), 7.03 (2H, d, *J* 8.4 Hz, ArH), 7.29 (2H, d, *J* 8.4 Hz, ArH), 8.20 (1H, br s, NH); MS (FAB): *m/z* 500 (MH^+).

*4.2.4. [2-(tert-Butoxycarbonylaminomethyl)-3-cyano-4-methylsulfanyl-6-naphthalen-2-yl-phenyl]-carbamic acid tert-butyl ester (**3d**)*

White amorphous solid; mp 159–160 °C. [Found: C, 67.08; H, 6.48; N, 8.29. $C_{29}H_{33}N_3O_4S$ requires: C, 67.03; H, 6.40; N, 8.09%.] ν_{max} (KBr) 3339, 2220, 1711 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.25 (9H, s, Boc), 1.46 (9H, s, Boc), 2.57 (3H, s, SCH_3), 4.45 (2H, s, CH_2), 5.56 (1H, br s, NH), 7.31 (1H, s, ArH), 7.49–7.52 (3H, m, ArH), 7.84–7.90 (4H, m, ArH), 8.20 (1H, br s, NH); MS (FAB): *m/z* 520 (MH^+).

*4.2.5. [2-(tert-Butoxycarbonylaminomethyl)-3-cyano-6-naphthalen-2-yl-4-piperidin-1-yl-phenyl]-carbamic acid tert-butyl ester (**3e**)*

White powder; mp 161–163 °C. [Found: C, 71.28; H, 7.32; N, 10.24. $C_{33}H_{40}N_4O_4$ requires: C, 71.20; H, 7.24; N, 10.06%.] ν_{max} (KBr) 3304, 2220, 1716 cm^{-1}; δ_H (300 MHz, CD_3OD) 1.17 (9H, s, Boc), 1.45 (9H, s, Boc), 1.62–1.64 (2H, m, CH_2, piperidinyl), 1.78–1.80 (4H, m, CH_2, piperidinyl), 3.19–3.21 (4H, m, CH_2, piperidinyl), 4.41 (2H, s, CH_2), 5.02 (1H, br s, NH), 7.11 (1H, s, ArH), 7.45–7.52 (3H, m, ArH), 7.86–7.91 (4H, m, ArH), 8.22 (1H, br s, NH); MS (FAB): *m/z* 557 (MH^+).

*4.2.6. [2-(tert-Butoxycarbonylaminomethyl)-3-cyano-4-(4-methylpiperidin-1-yl)-6-naphthalen-2-yl-phenyl]-carbamic acid tert-butyl ester (**3f**)*

White amorphous solid; mp 113–115 °C. [Found: C, 71.41; H, 7.32; N, 9.76. $C_{34}H_{42}N_4O_4$ requires: C, 71.55; H, 7.42; N, 9.82%.] ν_{max} (KBr) 3340, 2217, 1695 cm^{-1}; δ_H (300 MHz, CD_3OD) 0.90 (3H, d, *J* 6.0 Hz, CH_3), 1.33–1.35 (1H, m, CH, piperidinyl), 1.37 (9H, s, Boc), 1.45 (9H, s, Boc), 1.62–1.64 (2H, m, CH_2, piperidinyl), 1.65–1.69 (2H, m, CH_2, piperidinyl), 2.67–2.74 (2H, m, CH_2, piperidinyl), 3.44–3.48 (2H, m, CH_2, piperidinyl), 4.51 (2H, s, CH_2), 5.02 (1H, br s, NH), 7.00 (1H, s, ArH), 7.35–7.41 (3H, m, ArH), 7.76–7.80 (4H, m, ArH), 8.22 (1H, br s, NH); MS (FAB): *m/z* 571 (MH^+).

*4.2.7. [2-(tert-Butoxycarbonylaminomethyl)-3-cyano-4-morpholin-4-yl-6-naphthalen-2-yl-phenyl]-carbamic acid tert-butyl ester (**3g**)*

White amorphous solid; mp 127–128 °C. [Found: C, 68.64; H, 6.80; N, 10.23. $C_{32}H_{38}N_4O_5$ requires: C, 68.80; H, 6.86; N, 10.03%.] ν_{max} (KBr) 3337, 2218, 1714 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.16 (9H, s, Boc), 1.46 (9H, s, Boc), 3.01–3.12 (4H, m, CH_2, morpholinyl), 3.89–3.92 (4H, m, CH_2, morpholinyl), 4.44 (2H, s, CH_2), 5.56 (1H, br s, NH), 7.03 (1H, s, ArH), 7.48–7.52 (3H, m, ArH), 7.83–7.89 (4H, m, ArH), 8.20 (1H, br s, NH); MS (FAB): *m/z* 559 (MH^+).

*4.2.8. [2-(tert-Butoxycarbonylaminomethyl)-3-cyano-6-naphthalen-2-yl-4-(4-phenylpiperazin-1-yl)-phenyl]-carbamic acid tert-butyl ester (**3h**)*

White powder solid; mp 183–185 °C. [Found: C, 71.84; H, 6.72; N, 11.16. $C_{38}H_{43}N_5O_4$ requires: C, 72.01; H, 6.84; N, 11.05%.] ν_{max} (KBr) 3341, 2218, 1697 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.11 (9H, s, Boc), 1.46 (9H, s, Boc), 3.40 (8H, s, CH_2, piperazinyl), 4.46 (2H, s, CH_2), 5.56 (1H, br s, NH), 6.87–6.92 (1H, m, ArH), 6.97–6.99 (2H, m, ArH), 7.09 (1H, s, ArH), 7.29–7.32 (2H, m, ArH), 7.49–7.52 (3H, m, ArH), 7.84–7.90 (4H, m, ArH), 8.20 (1H, br s, NH); MS (FAB): *m/z* 634 (MH^+).

*4.2.9. [4′-Bromo-3-(tert-butoxycarbonylaminomethyl)-4-cyano-5-(4-phenylpiperazin-1-yl)-biphenyl-2-yl]-carbamic acid tert-butyl ester (**3i**)*

White powder; mp 179–180 °C. [Found: C, 61.46; H, 6.12; N, 10.38. $C_{34}H_{40}BrN_5O_4$ requires: C, 61.63; H, 6.08; N, 10.57%.] ν_{max} (KBr) 3329, 2218, 1697 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.25 (9H, s, Boc), 1.46 (9H, s, Boc), 3.38 (8H, s, CH_2, piperazinyl), 4.42 (2H, s, CH_2), 5.53 (1H, br s, NH), 6.80–6.99 (4H, m, ArH), 7.26–7.32 (4H, m, ArH), 7.54 (2H, d, *J* 8.10 Hz, ArH), 7.99 (1H, br s, NH); MS (FAB): *m/z* 662 (MH^+).

*4.2.10. [2-(tert-Butoxycarbonylaminomethyl)-3-cyano-4-dimethylamino-6-naphthalen-2-yl-phenyl]-carbamic acid tert-butyl ester (**3j**)*

White amorphous solid; mp 109–110 °C. [Found: C, 69.63; H, 7.18; N, 10.72. $C_{30}H_{36}N_4O_4$ requires: C, 69.74; H, 7.02; N, 10.84%.] ν_{max} (KBr) 3363, 2218, 1698 cm^{-1}; δ_H (300 MHz, CD_3OD) 1.16 (9H, s, Boc), 1.45 (9H, s, Boc), 3.04 (6H, s, NCH_3), 4.41 (2H, s, CH_2), 5.56 (1H, br s, NH), 7.05 (1H, s, ArH), 7.46–7.52 (3H, m, ArH), 7.86–7.90 (4H, m, ArH), 8.20 (1H, br s, NH); MS (FAB): *m/z* 517 (MH^+).

4.3. General procedure for the synthesis of 3-(aminomethyl)-4-cyano-5-(methylthio)biphenyl-ammonium ditrifluoroacetate (4a–c)

Compound **4** was obtained by stirring **3** (1 mmol) in a solution of 20% TFA in DCM (10 mL) at room temperature for 2 h. After completion of the reaction, TFA was removed under reduced pressure and residue was washed with DCM (3 mL) leaving a TFA salt of the product **4**.

*4.3.1. 3-(Aminomethyl)-4′-bromo-4-cyano-5-(methylthio)-biphenyl-2-ammonium ditrifluoroacetate (**4a**)*

White powder solid; mp >250 °C. [Found: C, 39.73; H, 2.94; N, 7.48. $C_{19}H_{16}BrF_6N_3O_4S$ requires: C, 39.60; H, 2.80; N, 7.29%.] ν_{max} (KBr) 3362 (NH), 2221 (CN), 1676 (CO) cm^{-1}; δ_H (300 MHz, DMSO-d_6) 2.40 (3H, s, SCH_3), 4.20 (2H, s, CH_2), 6.88 (1H, s, ArH), 7.04 (2H, d, *J* 8.4 Hz, ArH), 7.40 (2H, d, *J* 8.4 Hz, ArH); MS (FAB): *m/z* 348 (MH^+).

*4.3.2. 3-(Aminomethyl)-4-cyano-4′-methoxy-5-(methylthio)-biphenyl-2-ammonium ditrifluoroacetate (**4b**)*

White amorphous solid; mp >250 °C. [Found: C, 45.62; H, 3.76; N, 7.86. $C_{20}H_{19}F_6N_3O_5S$ requires: C, 45.54; H, 3.63; N, 7.97%.] ν_{max} (KBr) 3362, 2219, 1776 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 2.38 (3H, s, SCH_3), 3.81 (3H, s, OCH_3), 4.21 (2H, s, CH_2), 6.86 (1H, s, ArH), 7.06 (2H, d, *J* 8.4 Hz, ArH), 7.41 (2H, d, *J* 8.4 Hz, ArH); MS (FAB): *m/z* 300 (MH^+).

*4.3.3. 2-(Aminomethyl)-3-cyano-6-(naphthalen-2-yl)-4-(4-phenylpiperazin-1-yl)benzen ammonium ditrifluoroacetate (**4c**)*

White amorphous solid; mp >250 °C. [Found: C, 58.23; H, 4.58; N, 10.74. $C_{32}H_{29}F_6N_5O_5$ requires: C, 58.09; H, 4.42; N, 10.59%.] ν_{max} (KBr) 3364, 2219, 1697 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.07 (8H, s, CH_2, piperazinyl), 4.20 (2H, s, CH_2), 6.76–6.81 (1H, m, ArH), 6.97–7.00 (2H, m, ArH), 7.11 (1H, s, ArH), 7.20–7.25 (2H, m, ArH), 7.56–7.62 (3H, m, ArH), 7.96–8.05 (4H, m, ArH); MS (FAB): *m/z* 434 (MH^+).

4.4. General procedure for the synthesis of 1-*tert*-butoxycarbonyl-6-*sec*-amino-8-aryl-5-cyano-2-*oxo*-1,2,3,4-tetrahydroquinazolines (5a–e)

A mixture of **1** (1.0 mmol) and ketone **2** (288 mg, 1.0 mmol) in dry DMF (15 mL) was stirred at room temperature in the presence of KOH (276 mg, 2 mmol) for 3-4 h. The reaction mixture was diluted with distilled water and neutralized with 10% HCl. The solid precipitate thus formed was filtered, washed with excess of water, and purified by silica gel column chromatography using DCM as eluent.

*4.4.1. tert-Butyl 5-cyano-6-(dimethylamino)-8-(naphthalene-2-yl)-2-oxo-3,4-dihydroquinazoline-1(2H)-carboxylate (**5a**)*

White powder solid; mp 102–103 °C. [Found: C, 70.68; H, 5.88; N, 12.80. $C_{26}H_{26}N_4O_3$ requires: C, 70.57; H, 5.92; N, 12.66%.] ν_{max} (KBr) 1725, 1774, 2220 cm^{-1}; δ_H (300 MHz, CD_3OD) 1.56 (9H, s, Boc), 2.96 (6H, s, NCH_3), 4.98 (2H, s, CH_2), 6.99 (1H, s, ArH), 7.51–7.57 (3H, m, ArH), 7.90–8.03 (4H, m, ArH); MS (FAB): *m/z* 443 (MH^+).

*4.4.2. tert-Butyl 5-cyano-8-(naphthalen-2-yl)-2-oxo-6-(piperidin-1-yl)-3,4-dihydroquinazoline-1(2H)-carboxylate (**5b**)*

White powder solid; mp 192–194 °C. [Found: C, 72.29; H, 6.34; N, 11.76. $C_{29}H_{30}N_4O_3$ requires: C, 72.18; H, 6.27; N, 11.61%.] ν_{max} (KBr) 1720, 1772, 2220 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.57 (9H, s, Boc), 1.59–1.63 (2H, m, CH_2, piperidinyl), 1.75–1.83 (4H, m, CH_2, piperidinyl), 3.11–3.14 (4H, m, CH_2, piperidinyl), 5.02 (2H, s, CH_2), 6.93 (1H, s, ArH), 7.40–7.43 (1H, m, ArH), 7.55–7.61 (2H, m, ArH), 7.81–7.82 (1H, m, ArH), 7.85–7.92 (2H, m, ArH), 7.98 (1H, d, *J* 8.4 Hz, ArH); MS (FAB): *m/z* 483 (MH^+).

*4.4.3. tert-Butyl 5-cyano-8-(naphthalen-2-yl)-2-oxo-6-(4-phenylpiperazin-1-yl)-3,4-dihydroquinazoline-1(2H)-carboxylate (**5c**)*

White amorphous solid; mp 140–142 °C. [Found: C, 72.85; H, 6.10; N, 12.60. $C_{34}H_{33}N_5O_3$ requires: C, 72.97; H, 5.94; N, 12.51%.] ν_{max} (KBr) 1722, 1774, 2220 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.57 (9H, s, Boc), 3.33–3.41 (8H, m, CH_2, piperazinyl), 5.04 (2H, s, CH_2), 6.87–6.99 (4H, m, ArH), 7.25–7.31 (2H, m, ArH), 7.41–7.45 (1H, m, ArH), 7.57–7.62 (2H, m, ArH), 7.83–7.84 (1H, m, ArH), 7.88–7.93 (2H, m, ArH), 7.99 (1H, d, *J* 8.4 Hz, ArH); MS (FAB): *m/z* 560 (MH^+).

*4.4.4. tert-Butyl 5-cyano-6-morpholino-8-(naphthalen-2-yl)-2-oxo-3,4-dihydroquinazoline-1(2H)-carboxylate (**5d**)*

White amorphous solid; mp 158–160 °C. [Found: C, 69.54; H, 5.90; N, 11.66. $C_{28}H_{28}N_4O_4$ requires: C, 69.41; H, 5.82; N, 11.56%.] ν_{max} (KBr) 1722, 1772, 2222 cm^{-1}; δ_H (300 MHz, CD_3OD) 1.56 (9H, s, Boc), 3.16–3.19 (4H, m, CH_2, morpholinyl), 3.85–3.88 (4H, m, CH_2), 5.00 (2H, s, CH_2, morpholinyl), 6.95 (1H, s, ArH), 7.52–7.57 (3H, m, ArH), 7.92–8.04 (4H, m, ArH); MS (FAB): *m/z* 485 (MH^+).

*4.4.5. tert-Butyl 8-(4-bromophenyl)-5-cyano-2-oxo-6-(pyrrolidin-1-yl)-3,4-dihydroquinazoline-1(2H)-carboxylate (**5e**)*

White amorphous solid; mp 152–154 °C. [Found: C, 58.09; H, 5.14; N, 11.35. $C_{24}H_{25}BrN_4O_3$ requires: C, 57.95; H, 5.07; N, 11.26%.] ν_{max} (KBr) 1724, 1774, 2222 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.56 (9H, s, Boc), 1.99–2.03 (4H, m, CH_2, pyrrolidinyl), 3.56–3.60 (4H, m, CH_2, pyrrolidinyl), 4.97 (2H, s, CH_2), 6.64 (1H, s, ArH), 7.23 (2H, d, *J* 8.0 Hz, ArH), 7.62 (2H, d, *J* 8.0 Hz, ArH); MS (FAB): *m/z* 497 (MH^+).

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