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# Synthesis of highly functionalized 2,4-diaminoquinazolines as anticancer and anti-HIV agents

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ABSTRACT

Novel polyhalo 2,4-diaminoquinazolines **3a**–**3d** were prepared by reacting polyhaloisophthalonitriles with guanidine carbonate under solvent-free conditions and in the absence of a catalyst with good yields (74–95%). A series of highly functionalized 2,4-diaminoquinazolines **4**–**5** were then synthesized based on **3a**–**3c**. The anticancer activities of compounds **3**–**5** were evaluated in vitro against human cell lines such as Skov-3, HL-60, A431, A549, and HepG-2. Some of the compounds showed excellent cytotoxic activity and **5a** was found to be the most potent derivative, with an $IC_{50}$ value lower than 2.5 μg/mL against the five tumor cell lines, making it more active than cisplatin. Representative compounds were also preliminarily evaluated as HIV-1 inhibitors in vitro, and **3c** showed the most potent anti-HIV-1 activity with $EC_{50}$ values of 0.6 and 1.6 μg/mL, and TI values of >59.6 and 66.6, respectively.

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Derivatives of 2,4-diaminoquinazoline are widely used as inhibitors of dihydrofolate reductase[1] to treat opportunistic infections[2] in acquired immuno-deficiency syndrome (AIDS) patients and are known to be effective as antitumor agents,[3] inhibitors of $\alpha_1$-adreno-receptors,[4] anti-bacterial drugs,[5] anti-microbials,[6] and so on.[7] The potent bioactivity and low toxicity of these derivatives have meant that they have received increasing attention from researchers.[8] Several methods have been used to synthesize 2,4-diaminoquinazolines, including substitution of 2-aminobenzonitrile reacted with cyanamide, cyanoguanidine, chloroformamidine hydrochloride, and guanidine,[9] or 2-fluorobenzonitrile condensation with guanidine.[8,10] However, these procedures usually have shortcomings such as low yields and impractical conditions, and the introduction of multiple substituents into the 2,4-diaminoquinazoline ring often requires multistep reactions and complex experimental processes. To our knowledge, the availability of procedures to prepare highly functionalized and diverse 2,4-diaminoquinazoles is limited.

Polyhaloisophthalonitriles, particularly polyfluoro isophthalonitriles, have been widely used as organic agents.[11] Fluorine incorporation into biologically active compounds can alter drug metabolism or enzyme substrate recognition.[12] The hydrophobic nature of fluorinated compounds has also been cited for its ability to improve transport across the blood–brain barrier. Improved oral bioavailability is seen in some systems where fluorine substitution leads to improved hydrolytic stability. Due to the unique effects of F-substituents in pharmaceutical formulations, the use of fluorinated heterocyclic compounds as bioactive or functional molecules has recently increased.

To explore the biological activity of this type of derivative, an efficient and concise approach to constructing fluorine-containing or highly functionalized 2,4-diaminoquinazolines is necessary. At the same time, the halo-atoms of polyhalo 2,4-diaminoquinazoline **3** can be employed in nucleophilic substitution with nucleophiles. The cyano group can also be modified into an amido or carboxyl group, providing many opportunities for constructing more molecular libraries for biological activity screening.

In this study, an efficient method for the rapid generation of libraries of 2,4-diaminoquinazolines **3–5** based on the results of reacting polyhaloisophthalonitrile **1** with guanidine carbonate under solvent-free conditions was developed. Initially, polyhaloisophthalonitrile **1a** was reacted with guanidine carbonate **2** in different solvents, including acetonitrile, tetrahydrofuran (THF), 1,4-dioxane, and *N*,*N*-dimethylformamide (DMF), under different conditions. It was found that the intact starting materials were completely recovered when the reaction mixture was refluxed in certain solvents like acetonitrile, THF, 1,4-dioxane, whereas other solvents such as DMF gave unidentified products without forming the desired product **3a**. This may be because the limited solubility of **2** in acetonitrile, THF or 1,4-dioxane may have depressed the reaction, and the temperature was not high enough to initiate

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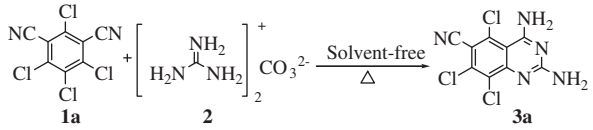
the reaction in the case of a solvent with a low boiling point like acetonitrile. While the ease of forming intramolecular H-bonding between **2** with a polar aprotic solvent such as DMF may retard further reaction of **1a** with **2,** on the other hand, a high temperature would cause the reaction to become complicated, resulting in side reactions, for instance, decomposition of the substrates, or the products, and hydrolysis. We fortuitously found that a solvent-free process works well when the reaction is performed by simply grinding **1a** with an almost-equal amount of guanidine carbonate **2** (ratio of 1:1.3) under solvent-free conditions at ca. 110 °C for 60 min (Scheme 1 and Table 1). Such a reaction produced **3a** at an 85% isolated yield (Table 1, entry 1).

In order to facilitate the operational program, accelerate the reaction, and improve the accuracy of the temperature, microwave irradiation (MW) was used to examine the practicality of the solvent-free synthetic route (Table 1). To this end, a set of experiments was carried out using polyhaloisophthalonitrile **1a** and guanidine carbonate **2** as model substrates. The mixture, composed of a 1:1.3 ratio of **1a** to **2**, was subjected to microwave irradiation in solvent-free conditions (Table 1, entries 2–10). The results show that the optimum reaction conditions required to obtain the product **3a** are a temperature of 110 °C and irradiation for 10 min at a maximum power of 200 W (Table 1, entry 6).

The compounds **1b**–**1d** were then reacted with guanidine carbonate under the same conditions (Scheme 2). The reactions took only 10 min to complete at 110 °C with a maximum power of 200 W of MW, and gave moderate to good yields (Table 2, entries 1–4).[13] The different structures of polyhaloisophthalonitrile had a clear influence with regard to their reactivity and yield (Table 2, entries 1–4).

The reactivity of **1** was increased by the electron-attracting properties of the group on the aromatic ring. As such, **1c** was generally the best substrate. Under the experimental conditions, the

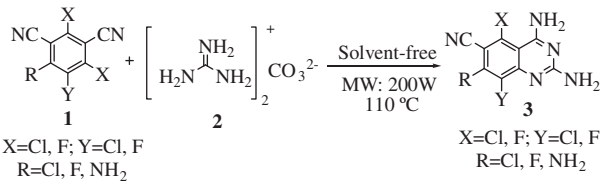



**Scheme 1.** Synthesis of **3a** under solvent-free conditions.

**Table 1**
Synthesis of **3a** under solvent-free conditions

| Entry | Power | *T* (°C) | Time (min) | Yield[a] (%) |
|---|---|---|---|---|
| 1 | Grinding | 110 | 60 | 85 |
| 2 | MW/180 W | 100 | 10 | 80 |
| 3 | MW/180 W | 110 | 10 | 83 |
| 4 | MW/180 W | 120 | 10 | 84 |
| 5 | MW/200 W | 100 | 10 | 82 |
| 6 | MW/200 W | 110 | 10 | 89 |
| 7 | MW/200 W | 120 | 10 | 85 |
| 8 | MW/220 W | 100 | 10 | 83 |
| 9 | MW/220 W | 110 | 10 | 88 |
| 10 | MW/220 W | 120 | 10 | 84 |

[a] Isolated yield based on polyhaloisophthalonitrile **1a**.

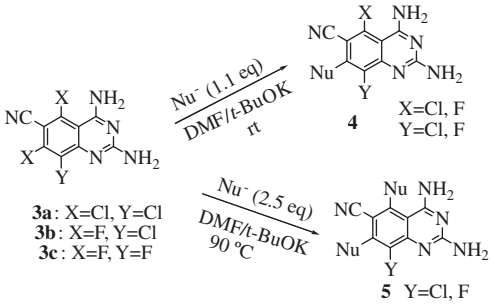



**Scheme 2.** Synthesis of compounds **3a–3d** by solvent-free reaction.

**Table 2**
Synthesis of **3** in solvent-free conditions under microwave irradiation

| Entry | **1** | X | Y | R | **3** | MW | *T* (°C) | Time (min) | Yield[a] (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | Cl | Cl | Cl | **3a** | 200 W | 110 | 10 | 89 |
| 2 | **1b** | F | Cl | F | **3b** | 200 W | 110 | 10 | 92 |
| 3 | **1c** | F | F | F | **3c** | 200 W | 110 | 10 | 95 |
| 4 | **1d** | Cl | Cl | $NH_2$ | **3d** | 200 W | 110 | 10 | 74 |

[a] Isolated yield based on polyhaloisophthalonitrile **1**.




**Scheme 3.** Synthesis of highly functionalized 2,4-diaminoquinazoline **4**–**5**.

reactivity ranking of the different structures of polyhaloisophthalonitrile was **1c** > **1b** > **1a** > **1d**.

To construct the diverse molecular library of highly functionalized 2,4-diaminoquinazolines, polyhalo 2,4-diaminoquinazoline **3** was reacted with a number of nucleophiles such as alkylamines, aryl amines, phenols, and mercaptans in DMF, at either room temperature or 90 °C under basic conditions, in order to replace the halo-atom with the nucleophile (Scheme 3 and Table 3). This type of reaction features an $S_NAr$ mechanism and forms the compound library **4**–**5** with good yields.[14,15]

In order to verify the structure of the highly functionalized 2,4-diaminoquinazolines, **5b** was selected as a representative compound and characterized via X-ray crystallography, as shown in Figure 1 (CCDC 760830).[16]

The novel 2,4-diaminoquinazolines **3**–**5** were evaluated for in vitro cytotoxic activity against a series of human cells according to a previously described method.[17] The tumor cell lines included ovarian carcinoma (Skov-3), myeloid leukemia (HL-60), epidermoid carcinoma (A431), lung adenocarcinoma (A549), and laryngeal car-

**Table 3**
Synthesis of 2,4-diaminoquinazoline **4**–**5**

| Entry | **3** | X | Y | **4** | Nu | Time (h) | Yield (%)[a] |
|---|---|---|---|---|---|---|---|
| 1 | **3b** | F | Cl | **4a** | PhNH | 10 | 61 |
| 2 | **3c** | F | F | **4b** | PhNH | 10 | 64 |
| 3 | **3b** | F | Cl | **4c** | *p*-MeOPhNH | 10 | 70 |
| 4 | **3c** | F | F | **4d** | *p*-ClPhNH | 10 | 69 |
| 5 | **3b** | F | Cl | **4e** | BnNH | 10 | 87 |
| 6 | **3c** | F | F | **4f** | BnNH | 10 | 89 |
| 7 | **3b** | F | Cl | **4g** | *t*-BuNH | 10 | 82 |
| 8 | **3c** | F | F | **4h** | *t*-BuNH | 10 | 88 |
| 9 | **3b** | F | Cl | **4i** | $Et_2N$ | 10 | 83 |
| 10 | **3c** | F | F | **4j** | $Et_2N$ | 10 | 85 |
| 11 | **3b** | F | Cl | **5a** | *n*-BuNH | 10 | 85 |
| 12 | **3c** | F | F | **5b** | *n*-BuNH | 20 | 90 |
| 13 | **3b** | F | Cl | **5c** | BnNH | 30 | 60 |
| 14 | **3c** | F | F | **5d** | BnNH | 15 | 78 |
| 15 | **3b** | F | Cl | **5e** | PhO | 10 | 79 |
| 16 | **3c** | F | F | **5f** | BnO | 30 | 82 |
| 17 | **3b** | F | Cl | **5g** | PhS | 30 | 82 |
| 18 | **3b** | F | Cl | **5h** | *n*-PrS | 15 | 73 |

[a] Isolated yield based on polyhalo 2,4-diaminoquinazoline **3**.

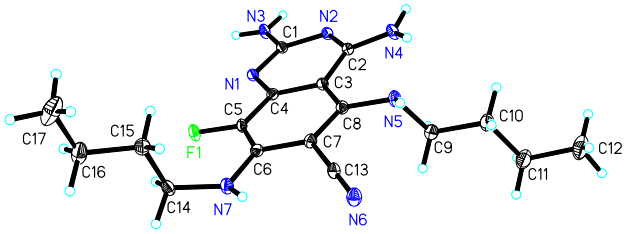



**Figure 1.** X-ray crystal structure of **5b**.

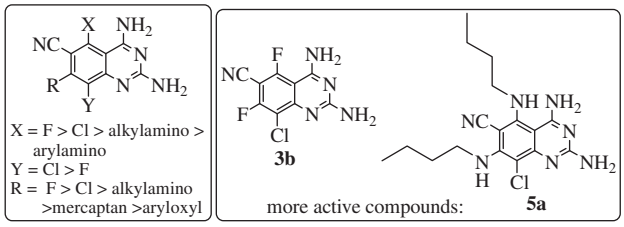



**Figure 2.** Structure–activity relationship of 2,4-diaminoquinazolines.

cinoma (HepG-2) cells. Cisplatin (DDP) was used as a positive control. The assay results are shown in Table 4 (where the $IC_{50}$ value is defined as the concentration of a compound that corresponds to 50% growth inhibition). As shown in Table 4, some of the compounds showed good activity against the tumor cells. In fact, **3b** was found to be more active than cisplatin against Skov-3, HL-60, and HepG-2 cells. In addition, the derivative **5a** was more active than cisplatin against HL-60, A549 and HepG-2 cells.

Comparison of the activities of the polyhalo 2,4-diaminoquinazolines **3**–**4** suggested that substitution at the 5- and 7-positions with fluorine atoms, and at the 8-position with a chlorine atom, plays a vital role in the modulation of cytotoxic activity. This would explain why **3b** showed excellent activity against the five tumor cells (Fig. 2 and Table 4, entry 2). Significantly, **3b** was up to 35 times more active than cisplatin against HL-60 cells (Table 4, entry 2 vs 23).

The polyhalo 2,4-diaminoquinazolines **3**–**4** showed poor activity against the tumor cell line A549 (Table 4, entries 1–14), and moderate or good activity against the Skov-3, HL-60, and A431 cells.

In addition, with the exception of **4c**, **4f** and **4h**, these compounds were found to be more active against HepG-2 cells than cisplatin (Table 4, entries 1–14 and Fig. 2).

With the exception of **5a** and **5b,** highly functionalized 2,4-diaminoquinazolines **5** showed poor or moderate activity against A549, A431, and HepG-2 cells and good activity against Skov-3 and HL-60 cells (Table 4, entries 15–22).

**Table 4**
Cytotoxic activities of 2,4-diaminoquinazoles **3**–**5** in vitro[a] ($IC_{50}$, μg/mL)[b]

| No. | Compound | Skov-3 | HL-60 | A431 | A549 | HepG-2 |
|---|---|---|---|---|---|---|
| 1 | **3a** | 1.3 | 19 | 3.3 | 29.7 | 2.5 |
| 2 | **3b** | 0.14 | 0.04 | 1.5 | 30.8 | 4.8 |
| 3 | **3c** | 8 | 51 | 105 | >1000 | 5.0 |
| 4 | **3d** | 0.8 | 6.7 | 9.5 | 188 | 3.7 |
| 5 | **4a** | 3.7 | 47 | 4.8 | >1000 | 5.9 |
| 6 | **4b** | 6.5 | 40 | 7.0 | >1000 | 1.4 |
| 7 | **4c** | 1.6 | 2.2 | 5.1 | 103 | 10.2 |
| 8 | **4d** | 4.8 | 35 | 4.5 | 115 | 1.0 |
| 9 | **4e** | 0.8 | 0.3 | 1.4 | 34.1 | 1.4 |
| 10 | **4f** | 11 | 14 | 12.9 | >1000 | 27.8 |
| 11 | **4g** | 2.1 | 5.2 | 6.5 | 313 | 5.4 |
| 12 | **4h** | 2.4 | 18 | 11.9 | >1000 | 16.2 |
| 13 | **4i** | 0.4 | 2.3 | 7.3 | 7.1 | 2.0 |
| 14 | **4j** | 1.0 | 6.4 | 16.4 | 26.5 | 1.3 |
| 15 | **5a** | 0.6 | 0.7 | 2.5 | 2.0 | 1.3 |
| 16 | **5b** | 1.6 | 1.4 | 1.0 | >1000 | 2.6 |
| 17 | **5c** | 3.7 | 8.5 | 716 | >1000 | 19.2 |
| 18 | **5d** | 2.5 | 7.2 | 20.7 | 13.9 | 13.4 |
| 19 | **5e** | 14 | 88 | >1000 | >1000 | >1000 |
| 20 | **5f** | 14 | 62 | 68.3 | >1000 | 84 |
| 21 | **5g** | 9.4 | 26 | 32.4 | >1000 | 5.0 |
| 22 | **5h** | 1.2 | 7.7 | 535 | >1000 | >1000 |
| 23 | Cisplatin (DDP) | 0.5 | 1.4 | 0.6 | 5.1 | 8.2 |

[a] The cytotoxicity, determined as $IC_{50}$ values for each cell line, is the concentration of compound that can reduce the optical density of treated cells by 50% with respect to untreated cells using the MTT assay.
[b] Data represent the mean values of three independent measurements.

We found that substitution at the 5- and 7-positions with *n*-BuNH, and at the 8-position with a chlorine atom, also plays an important role in regulating cytotoxic activity. This was evident when we observed that **5a** and **5b** showed good activity against the tumor cells used in our study (Table 4, entries 15–16 and Fig. 2).

The representative compounds **3a–3c**, **4a–4b** and **5g–5h** were subsequently evaluated for their inhibitory activity against HIV-1 replication in acutely infected C8166 cells in vitro, according to procedures described in the literature.[18] AZT was used as the reference compound. The results of the cytotoxicity studies are summarized in Table 5. The seven target compounds exhibited moderate activity against HIV-$1_{IIIB}$ with $EC_{50}$ values of 0.1–17.3 μg/mL and TI values of 7.0–66.6 (Table 5, entries 1–7). The number of fluorine atoms in the compounds influenced the activity and the toxicity of the tested compounds. The TI values of the corresponding compounds increased sharply (**3c** vs **3b** and **3a**; **4b** vs **4a**) as the number of fluoro atoms increased. Thus the TI values were ranked as **3c** > **3b** > **3a** (entries 1–3), **4b** > **4a** (entries 4 and 5), and **4g** ≈ **4h** (entries 6 and 7). Notably, **3c** was found to have the most potent anti-HIV-1 activity with $EC_{50}$ values of 0.6/1.6 μg/mL and TI = 59.6/66.6, respectively (entry 3). Therefore the introduction of fluoro-atoms at the 5-, 7-, and 8-positions of polyhalo 2,4-diaminoquinazolines could generally lead to more potent analogs.

In summary, an efficient, concise, and simple procedure for the preparation of a highly functionalized 2,4-diaminoquinazoline library was developed, and the library compounds produced were proven to have remarkably potent antitumor activity. The substitution at the 5- and 7-positions with *n*-BuNH or fluorine atoms, and at the 8-position with a chlorine atom, on the 2,4-diaminoquinazole ring, plays an important role in regulating cytotoxic activity. This makes the compounds **3b** and **5a** the most promising leads for future applications, pending further structural modifications based on the valuable information described here. In addition, **3c** exhibited the most significant anti-HIV-1 activity, which paves the way to finding promising leads for anti-HIV-1 in the future.

**Table 5**
Anti-HIV-1 replication activity in HIV-$1_{IIIB}$ infected C8166 cell lines[a,b]

| No. | Compound | $CC_{50}$[c] (μg/mL) | $EC_{50}$[d] | TI[e] |
|---|---|---|---|---|
| 1 | **3a** | 14.3/14.6 | 1.0/1.8 | 8.0/14.0 |
| 2 | **3b** | 3.9/4.0 | 0.1/0.6 | 7.0/32.8 |
| 3 | **3c** | 36.4/105.8 | 0.6/1.6 | 59.6/66.6 |
| 4 | **4a** | 6.3/8.6 | 0.4/0.6 | 13.5/15.7 |
| 5 | **4b** | 7.2/6.9 | 0.4/0.2 | 16.3/31.2 |
| 6 | **5g** | 51.0/46.8 | 3.2/4.4 | 10.6/15.8 |
| 7 | **5h** | >200/>200 | 13.3/17.3 | 11.5/15.1 |
| 8 | AZT[f] | 1145 | 0.004 | 286250 |

[a] All data presented are averages of at least three separate experiments.
[b] The data are from Ref. 18.
[c] $CC_{50}$ (50% cytotoxic concentration), concentration of drug that causes 50% reduction in total C8166 cell number.
[d] $EC_{50}$: concentration that inhibits HIV-$1_{IIIB}$ replication by 50%.
[e] In vitro therapeutic index TI = $CC_{50}/EC_{50}$.
[f] AZT was used as the reference compound.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.06.056.

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13. *General procedure for the synthesis of polyhalo 2,4-diaminoquinazoline* **3**: A dry mortar was charged with polyhaloisophthalonitrile **1** (1.5 mmol) and guanidine carbonate (2.0 mmol). The mixture was mixed at room temperature by vigorously grinding with a pestle for a few minutes (ca. 5 min). The mixture was placed in a microwave tube and irradiated in a microwave reactor (Discover), with control of power and temperature by infrared detection, at 110 °C for 10 min (maximum power 200 W). After cooling, the reaction mixture was poured into 25 mL of water and filtered to obtain the crude products, which were purified by column chromatography (petrol/ethyl acetate = 1:1–1:2, v/v) on silica-gel to give the desired products **3**. Compound **3a**: Yellow solid. Mp >300 °C. IR (KBr): 3457, 3392, 3323, 3204, 2225, 1532, 1562, 1086, 1172 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) $\delta$ 6.84 (br, 1H, $NH_2$), 7.09 (br, 1H, $NH_2$), 7.41 (br, 1H, $NH_2$), 7.95 (br, 1H, $NH_2$). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) $\delta$ 104.2, 107.8, 115.0, 126.8, 135.2, 135.5, 161.0, 161.7, 162.3. HRMS (TOF ES$^+$): *m/z* calcd for $C_9H_5Cl_3N_5$ [(M+H$^+$)], 287.9605; found, 287.9608. Compound **3b**: Yellow solid. Mp >300 °C. IR (KBr): 3479, 3377, 3160, 2239, 1630, 1561, 1399, 1092, 834 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.05 (br, 1H, $NH_2$), 7.34 (br, 2H, $NH_2$), 7.41 (br, 1H, $NH_2$), 8.19 (br, 1H, $NH_2$). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) $\delta$ 82.1, 98.0, 109.7, 110.9, 155.8, 161.1, 159.2 (d, *J* = 267.0 Hz), 160.6, 162.2 (d, *J* = 265.0 Hz), 163.9. HRMS (TOF ES$^-$): *m/z* calcd for $C_9H_3ClF_2N_5$ [(M−H$^+$)], 254.0051; found, 254.0050.
14. *General procedure for the preparation of products* **4**: A 25 mL round-bottom flask was charged with polyhalo 2,4-diaminoquinazoline **3** (1 mmol), *N*,*N*-dimethylformamide (10 mL) and *t*-BuOK (1.5 mmol), then the solution was added to nucleophile (1.1 mmol). The mixture was stirred at room temperature until TLC indicated complete consumption of the starting **3**. The mixture was quenched by the addition of water (20 mL), and then EtOAc (30 mL) was added. The organic phase was washed with water (10 mL × 2), dried over $Na_2SO_4$, concentrated and purified by flash column chromatography, to afford the final product **4** in 61–89% yield. Compound **4a**: light yellow solid. Mp 279–283.5 °C. IR (KBr): 3471, 3384, 3140, 2224, 1662, 1600, 1555, 1504, 1468, 1366, 1242, 842 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) $\delta$ 6.97–7.26 (m, 8H, Ar, $NH_2$), 7.83 (br, 1H, $NH_2$), 8.45 (br, 1H, NH). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) $\delta$ 86.2 (d, *J* = 18.8 Hz), 96.0, 112.8, 114.4, 118.9, 1122.1, 129.3, 143.0, 143.2, 154.7, 160.2, 162.8 (d, *J* = 245.0 Hz), 163.2. HRMS (TOF ES$^+$): *m/z* calcd for $C_{15}H_{11}ClFN_6$ [(M+H$^+$)], 329.0712; found, 329.0717.
15. *General procedure for the preparation of products* **5**: A 25 mL round-bottom flask was charged with polyhalo 2,4-diaminoquinazoline **3** (1 mmol), *N*,*N*-dimethylformamide (10 mL) and *t*-BuOK (3.0 mmol), then the solution was added to nucleophile (2.5 mmol). The mixture was stirred at 90 °C until TLC indicated complete consumption of the starting **3**. The mixture was quenched by the addition of water (20 mL), and then EtOAc (30 mL) was added. The organic phase was washed with water (10 mL × 2), dried over $Na_2SO_4$, concentrated and purified by flash column chromatography, to afford the final product **5** in 73–90% yield. Compound **5a**: Light yellow solid. Mp 127–130 °C. IR (KBr): 3413, 3205, 2959, 2920, 2203, 1594, 1462, 1392, 1113, 796 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) $\delta$ 0.74–0.86 (m, 6H, $CH_3$), 1.28–1.30 (m, 4H, $CH_2$), 1.50–1.54 (m, 4H, $CH_2$), 2.99–3.00 (m, 2H, $NCH_2$), 3.52–3.54 (m, 2H, $NCH_2$), 4.80 (br, 1H, NH), 5.64 (br, 1H, NH), 6.55 (br, 2H, $NH_2$), 7.74 (br, 2H, $NH_2$). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) $\delta$ 14.0, 19.6, 20.0, 32.3, 32.6, 45.4, 51.1, 86.4, 98.4, 105.9, 118.0, 147.9, 153.3, 153.8, 162.3. HRMS (TOF ES$^-$): *m/z* calcd for $C_{17}H_{23}ClN_7$ [(M−H$^+$)], 360.1709; found, 360.1709.
16. CCDC 760830 contains the supplementary crystallographic data for compound **5b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
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