Synthesis of aniline analogs containing different secondary amines

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Abstract: Aniline analogs containing different secondary amines are important intermediates of small molecule anticancer drugs. In this work, a rapid synthetic method for target compounds was established. Compounds 2a-c were synthesized from *p*-nitrochlorobenzene through two steps including reduction reaction and nucleophilic substitution. The structure of the target compounds was confirmed by ^{1}H NMR and MS spectrum. Furthermore, the synthetic method was optimized. The total yield of the two steps was up to 56%.

1. Introduction

Despite significant advances in biological research and the development of new diagnostic and therapeutic strategies, cancer still remains one of the leading causes of death [1]. Nowadays, in addition to surgical removal of tumors, conventional radiotherapy and chemotherapy are the main methods of cancer treatment [2]. Chemotherapy and radiotherapy can kill cancer cells on a large scale, but the recovery rate is low because they can't distinguish tumor cells from normal cells. Targeted therapy could target specifically targets of tumor cells to reduce side effects to normal tissue. In addition, many cancers have developed resistance to above therapies, which makes the next treatment ineffective [3]. In recent years, tremendous efforts have been made to develop new treatments aimed at improving the specific targeting of cancer cells and overcoming resistance to current therapies.

Aniline analogs (2a-c) containing different secondary amines are key intermediates and are wildly used in the pharmaceutical chemical and other fields. In recent years, many small molecule targeted antitumor drugs had been reported. Among them, many molecules possessing potent biological activity contained the fragment of aniline analogs (2a-c) with different secondary amines. Therefore, design and synthesis of aniline analogs with different secondary amines (2a-c) played a great role in the study of anticancer drugs. The structures of these compounds were shown in Fig.1 such as 4-(4-methylpiperazin-1-yl) aniline (2a) [4-6], N^1-(2-(dimethylamino) ethyl)-N^1-methylbenzene-1, 4-diamine (2b) [7-8], 4-morpholinoaniline (2c) [9-11].

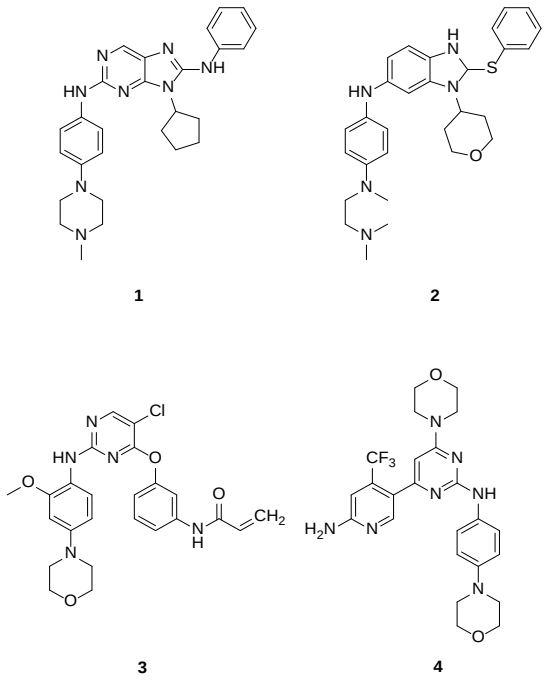

Fig 1. Structures of the active compounds containing aniline analogs.

2. Materials and methods

NMR spectra were performed using Bruker 400 MHz spectrometers (Bruker Bioscience, Billerica, MA, USA) with TMS 210 as an internal standard. Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC–MS (Agilent, Palo Alto, CA, USA). All the materials were obtained from commercial suppliers and used without purification, unless otherwise specified. Yields were not optimized. TLC analysis was carried out on silica gel plates GF254 (Qindao Haiyang Chemical, China).

3. Synthesis of compounds

The structures and the synthetic route of compounds were shown in Fig 2.

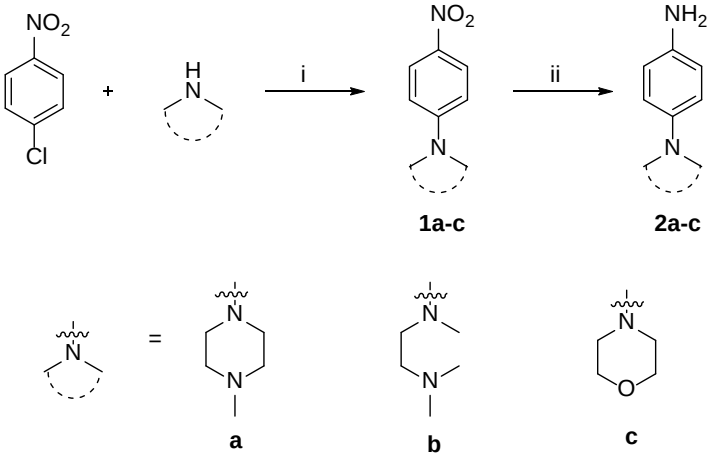

Fig 2. The synthetic route of compound 2a-c.

Reagents and conditions: (i) DMF, DIPEA, 130 °C, reflux, 12 h; (ii) EtOH, $FeCl_3$•$6H_2O$, $N_2H_4 \cdot H_2O$, active carbon, 80 °C, reflux, 12 h.

3.1 Preparation for 1-methyl-4-(4-nitrophenyl) piperazine (1a)

P-nitrochlorobenzene (1.0 g, 6.34 mmol) and *N*-methylpiperazine (1.2 g, 12.00 mmol) were dissolved in *N, N*-dimethylformamide (10mL). Then *N, N*-diisopropylethylamine (1.6 g, 12.38 mmol) was added into the mixture. And the mixture was refluxed at 130 °C for 12 hours, and then the reaction was monitored by TLC analysis. After the mixture cooled to room temperature, then it was stopped by adding suitable water and ethyl acetate of twice the amount. The combined organic layer was dried over anhydrous Na_2SO_4. Concentrate the organic layer under vacuum to afford a crude product. The product was purified by silica gel chromatography, to obtain a light yellow solid (1.05 g, 75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, *J* = 9.5 Hz, 2H), 7.02 (d, *J* = 9.5 Hz, 2H), 3.52-3.41 (m, 4H), 2.48-2.39 (m, 4H), 2.22 (s, 3H). MS (ESI): m/z [M+H] + 222.1.

3.2 Preparation for N^1, N^1, N^2-trimethyl-N^2-(4-nitrophenyl) ethane-1, 2-diamine (1b)

The experimental method is similar to the preparation of 1a. (0.93 g, 65.4%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, *J* = 9.5 Hz, 2H), 6.77 (d, *J* = 9.5 Hz, 2H), 3.57 (t, *J* = 6.9 Hz, 2H), 3.07 (s, 3H), 2.43 (t, *J* = 6.9 Hz, 2H), 2.20 (s, 6H). MS (ESI): m/z [M+H] + 224.1.

3.3 Preparation for 4-(4-nitrophenyl) morpholine (1c)

The experimental method is similar to the preparation of 1a. (1.07 g, 81%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, *J* = 9.4 Hz, 2H), 7.04 (d, *J* = 9.6 Hz, 2H), 3.76-3.71 (m, 4H), 3.41 (t, *J* = 4.9 Hz, 4H). MS (ESI): m/z [M+H] + 209.1.

3.4 Preparation for 4-(4-methylpiperazin-1-yl) aniline (2a)

1-methyl-4-(4-nitrophenyl) piperazine (1.0 g, 4.52 mmol) and ferric chloride hexahydrate (1.2 g, 4.52 mmol) were dissolved in ethanol (10 mL). Then active carbon (0.3 g, 22.60 mmol) and hydrazine hydrate (1.8 g, 36.16 mmol) was added into the mixture. And the mixture was refluxed at 80 °C for 12 hours. The reaction was monitored by TLC analysis. After the filtration of solvent, the filtrate was concentrated under reduced pressure, and then dried to obtain a yellow solid (0.69 g, 79.5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.78 (d, *J* = 8.8 Hz, 2H), 6.61 (d, *J* = 8.8 Hz, 2H), 3.26 (s, 6H), 2.78 (s, 3H), 2.52 (t, *J* = 1.9 Hz, 4H). MS (ESI): m/z [M+H] + 192.1.

3.5 Preparation for N^1-(2-(dimethylamino) ethyl)-N^1-methylbenzene-1, 4-diamine (2b)

The experimental method is similar to the preparation of 2a. (0.62 g, 71.5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (s, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 3.73 (d, *J* = 8.0 Hz, 2H), 3.12 (d, *J* = 19.2 Hz, 2H), 2.89 (s, 3H), 2.76 (s, 6H). MS (ESI): m/z [M+H] + 194.1.

3.6 Preparation for 4-morpholinoaniline (2c)

The experimental method is similar to the preparation of 2a. (0.76 g, 89%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.76 (d, *J* = 8.4 Hz, 2H), 6.65 (d, *J* = 8.5 Hz, 2H), 6.19 (s, 2H), 3.72–3.66 (m, 4H), 2.98–2.88 (m, 4H). MS (ESI): m/z [M+H] + 179.1.

4. Conclusions

In conclusion, three aniline analogs containing different secondary amines were synthesized from the commercially available *p*-nitrochlorobenzene through two steps of nucleophilic substitution and reduction reactions. Its structure was confirmed by ^{1}H NMR spectrum. The purity of the product was high.

Acknowledgments

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