Synthesis of 5-oxo-*N*, 1-diphenyl-2, 5-dihydro-1*H*-pyrazole-3-carboxamide

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Abstract: 5-oxo-*N*, 1-diphenyl-2, 5-dihydro-1*H*-pyrazole-3-carboxamide, is an important intermediate for many c-Met inhibitors. In this paper, a rapid and high yield synthetic method for compound 10 was established. Compound 10 was optimized from phenylhydrazine by condensation, oxidation reaction and nucleophilic substitution. The structure of the target compound 10 was confirmed by ^{1}H NMR and MS spectrum. The synthetic method was optimized.

1. Introduction

Hepatocyte growth factor (HGF) is a pleiotropic growth factor that can promote the movement, division, growth and angiogenesis of cells [1]. The c-mesenchymal-epithelia transition factor (c-Met), known as hepatocyte growth factor receptor (HGFR), which belongs to the receptor tyrosine kinases (RTKs) subfamily [2]. Hepatocyte growth factor (HGF) can selectively bind to the c-mesenchymal-epithelia transition factor (c-Met). Receptor tyrosine kinase (c-Met) is expressed in malignant or normal cells and is closely related to the growth of some organs such as brain, kidney, skin, lung, etc. Previous studies have shown that c-Met can induce various signaling pathways to mediate the differentiation, migration, proliferation and survival of cells. Abnormal c-Met signal activation is often caused by gene amplification, rearrangement, point mutation and autocrine or paracrine HGF stimulation, which is related to many types of human malignant tumors. Therefore, c-Met has become a promising target for cancer treatment [3-7]. However, the acquired resistance of tumor cells to tyrosine kinase inhibitors was caused by secondary mutations or gene amplification of cells. Although many anti-tumor drugs have been developed, no effective drug has been found to overcome such problems [8-10]. Therefore, we need to continue to research and optimize anti-tumor inhibitors.

Nowadays, many small molecule anti-tumor drugs have been reported. Among them, many molecule inhibitors contain the structure of 5-oxo-*N*, 1-diphenyl-2, 5-dihydro-1*H*-pyrazole-3-carboxamide (10). For example, *N*-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide(1) with improved selectivity profiles over VEGFR-2 and IGF-1R that could serve as useful tools to probe the relationship between kinase selectivity and in vivo efficacy in tumor xenograft models [11], 1,5-dimethyl-3-oxo-*N*-(5-((2-((1-phenoxyvinyl) amino) pyridin-4-yl) oxy) pyridin-2-yl)-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (2) which is useful in modulating the protein tyrosine kinase activity, and in modulating cellular activities such as proliferation, differentiation, apoptosis, migration and invasion [12], *N*-(5-hydroxypyridin-2-yl)-2,5-dimethyl-3-oxo-1-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (3) [13], *N*-(5-((2-(3-(2-hydroxyethyl) ureido) pyridin-4-yl) oxy) pyridin-2-yl) -1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (4) [12]. The structures of these compounds were shown in Fig.1.

Therefore, the development and synthesis of 5-oxo-*N*, 1-diphenyl-2, 5-dihydro-1*H*-pyrazole-3-carboxamide (10) derivatives play an important role in the research of the novel c-Met inhibitors. In this article, we found an effective synthetic method for 5-oxo-*N*, 1-diphenyl-2, 5-dihydro-1*H*-pyrazole-3-carboxamide (10). In the whole process, the target compound 10 was synthesized by condensation, oxidation reaction and nucleophilic substitution, making it more suitable for industrial production [11, 14]. The structures and the synthetic route were shown in Fig 2.

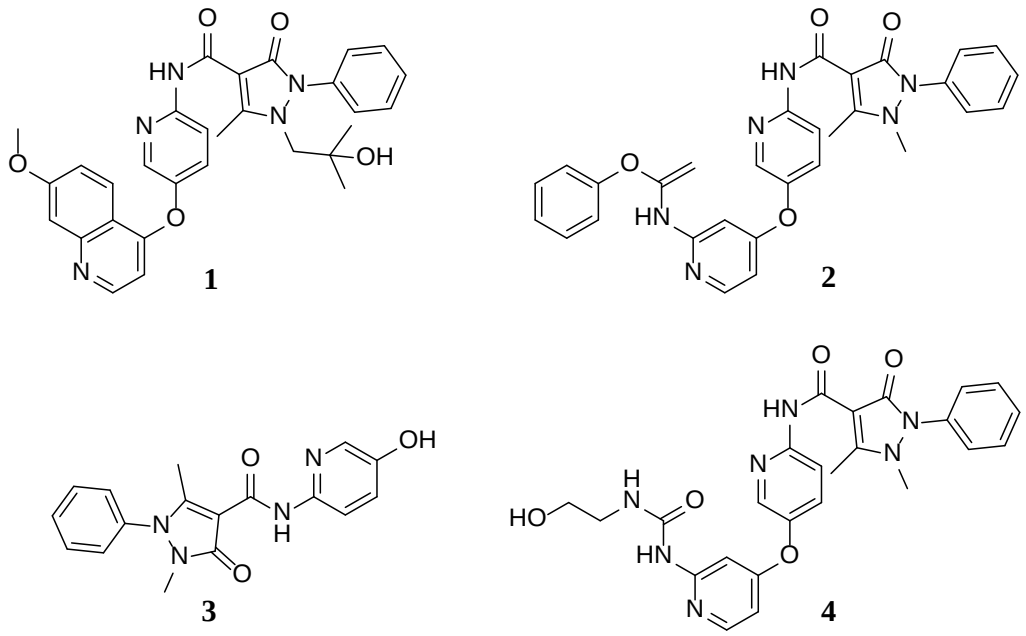

Fig 1. Some representative c-Met inhibitors bearing the intermediate.

2. Materials and methods

NMR spectra were performed using Bruker 400 MHz spectrometers (Bruker Bioscience, Billerica, MA, USA) with TMS 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 were shown in Fig.2.

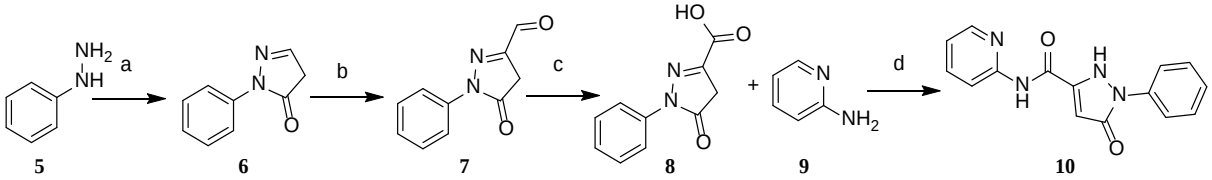

Fig 2. The synthetic route of compound 10.

Reagents and conditions: (a) 3-oxopropanoic acid, AcOH, 110 ^{o}C; (b) $POCl_3$, DMF, 48 h, r.t.; (c) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, 80 ^{o}C, 48 h; (d) $(COCl)_2$, DMF, DIPEA, CH_2Cl_2, 3 h.

3.1 Preparation for 2-phenyl-2, 4-dihydro-3H-pyrazol-3-one (6)

Compound 5 (7.5 g, 85.2 mmol) and 3-oxopropanoic acid (9.2 g, 85.2 mmol) were dissolved in acetic acid (80 mL). The reaction mixture was stirred at 110°C until TLC thin layer technique showed that the starting material had been completely consumed. The mixture was evaporated under reduced pressure to remove the solvent. After cooling to room temperature, the reaction was quenched by adding water. The solid was filtered and washed with ice-cold ethanol. After purification by column chromatography, the white solid compound 2-phenyl-2, 4-dihydro-3H-pyrazol-3-one (6) was obtained. Yield 75.6%. MS (ESI): m/z 161.06 $[M+H]^+$.

3.2 Preparation for 5-oxo-1-phenyl-4, 5-dihydro-1H-pyrazole-3-carbaldehydedine (7)

A mixture of $POCl_3$ (3 mL, 41.75 mmol) and DMF (5.55 g, 0.04 mol) was stirred at 0 ^{o}C for 1 h under the protection of gas N_2. Compound 6 was dissolved in the above mixture, and stirred

continuously at room temperature for 48 hours. After the reaction was completed, the reaction solution was poured into an aqueous solution and adjusted to be weakly basic, and extracted three times with methylene chloride (100 mL). The organic layer was collected, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the compound 5-oxo-1-phenyl-4, 5-dihydro-1*H*-pyrazole-3-carbaldehydedine (**7**). Yield 80.5%. MS (ESI): m/z 189.06 $[M+H]^+$.

3.3 Preparation for 5-oxo-1-phenyl-4, 5-dihydro-1*H*-pyrazole-3-carboxylic acid (8)

To a 100 mL round-bottomed flask cooled to 0 °C was added Compound **7** (0.28 g, 1 mmol), t-BuOH (5 mL) and 2-methyl-2-butene (2.2 mL, 20.9 mmol) under ice bath conditions. $NaClO_2$ (0.38 g, 4.2 mmol) was added dropwise to the mixed solution, and then the aqueous of KH_2PO_4 (1.2 g, 8.3 mmol) was added. The biphasic mixture was warmed to room temperature and stirred until TLC thin layer technique showed that the starting material had been completely consumed. The mixture was rotavaped under reduced pressure to remove the solvent. After extracted three times with ethyl acetate (100 mL), The organic layer was collected, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the compound 5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazole-3-carboxylic acid (8) as yellow solid in 84.7% yield. MS (ESI): m/z 205.05 $[M+H]^+$.

3.4 Preparation for 5-oxo-*N*, 1-diphenyl-2, 5-dihydro-1*H*-pyrazole-3-carboxamide (10)

Compound 8 (0.11 g, 0.04 mol) was dissolved in CH_2Cl_2 (10 mL). *N*, *N*-dimethylformamide (1 d) and Oxalyl chloride was added dropwise to the solution until TLC showed the raw materials was completely consumed. The reaction solution was transferred to a mixture of compound **9** in methylene chloride and *N*, *N*-diisopropylethylamine (5 d). The mixture was stirred at room temperature for 3 h. The reaction was concentrated under reduced pressure to obtain the crude product. The crude product was recrystallized from isopropanol and petroleum ether to afford 5-oxo-1-phenyl-4, 5-dihydro-1*H*-pyrazole-3-carboxylic acid (10), as yellow solid in 90.5% yield. MS (ESI): m/z 280.10 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 8.44 (s, 1H), 8.38 (s, 1H), 7.96 (s, 3H), 7.40 (t, J = 7.8 Hz, 2H), 7.30 (s, 1H), 7.18 (t, J = 7.4 Hz, 1H), 3.42 (s, 2H).

4. Conclusion

In Conclusion, the synthesis of 5-oxo-*N*, 1-diphenyl-2, 5-dihydro-1H-pyrazole-3-carboxamide (10) from phenylhydrazine was optimized by four steps of condensation reaction, oxidation reaction and nucleophilic substitution reaction. After using the optimized reaction conditions and synthesis methods, the yield of intermediate 10 was obviously improved. This work was hopeful to provide a valuable reference for the synthesis of c-Met inhibitors. The structure of compound 5-oxo-*N*, 1-diphenyl-2, 5-dihydro-1H-pyrazole-3-carboxamide (10) was confirmed by MS and ^1H NMR spectroscopy.

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