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(*E*)-3-(dimethylamino)-1-(1*H*-indol-3-yl)prop-2-en-1-one

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Abstract. (*E*) -3- (dimethylamino) -1- (1*H*-indol-3-yl) prop-2-en-1-one (4) is an important intermediate in many biologically active compounds such as osimertinib. In this work, compound (4) was synthesized through three steps, using 1H-indole as starting material. The synthetic method of 4 was optimized and can be used to synthesize the derivatives of (*E*) -3- (dimethylamino) -1- (1*H*-indol-3-yl) prop-2-en-1-one. And the structure of (*E*)-3- (dimethylamino) -1-(1*H*-indol-3-yl) prop-2-en-1-one is confirmed by MS and ^{1}HNMR spectrum.

Introduction

Cancer is disease caused by the loss of normal regulation and over proliferation of cells in the bod[1]. Over-proliferation of cells called cancer cells, cancer cells can often encroach on the surrounding tissue, and even the body's circulatory system and / or lymphatic system can be transferred to other parts of the body [2]. Although there are many drugs currently used for the treatment of cancer through taking and surgery, the problem of poor drug treatment and recurrence of cancer remains to be solved urgently [3-4].To address the clinical challenge of drug resistance, the third generation of the EGFR TKI, which has been developed as a parent, can selectively act on EGFR T790M and the third generation EGFR TKI and cysteine 797 form at the ATP binding site Covalent bond. Early clinical trials have demonstrated the efficacy of the third generation of EGFR TKIs in patients with dual-mutant tumors (EGFR L858R / T790M and ex19del / T790M) and first-generation EGFR-TKI acquired resistance. Hydrophobic interaction between a large number of methionine residues in EGFR T790M and pyrimidine ring-based drugs may result in the specificity of such drugs to EGFR T790M.

In recent years, many small-molecule anti-cancer drugs have been reported. Among them, (*E*) -3- (dimethylamino) -1- (1*H*-indol-3-yl) prop-2-en-1-one is an important intermediate for the synthesis of various active compounds. Therefore, a (*E*) -3- (two methyl amino) -1- (1*H*-indole -3- base) propyl -2-ene -1- ketone has been designed and synthesized in the study of anticancer drugs.

Many (*E*)-3-(dimethylamino)-1-(1*H*-indol-3-yl)prop-2-en-1-one derivatives which exhibited potential biological activities[5]. Such as *N*-(2-((2-(dimethylamino) ethyl)(methyl)amino)-4-methoxy-5-((4-(1-methyl-1*H*-indol-3-yl)pyrimidin-2-yl)amin o)phenyl)acrylamide(1),N-(3-((2-((4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl)amin o)-5-(trifluoromethyl)pyrimidin-4-yl)oxy)phenyl)acrylamide(2)[6-7],*N*-(3-((5-chloro-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)oxy)phenyl)a crylamide(3)[8-9].These three drugs are the third generation of EGFR-TKI , have a good therapeutic effect on cancer. The treatment of T790M and L858R mutations is

much better than the second generation of EGFR-TKI. Therefore, (*E*)-3-(dimethylamino) -1- (1*H*-indol-3-yl) prop-2-en-1-one (4) is a very important intermediate.

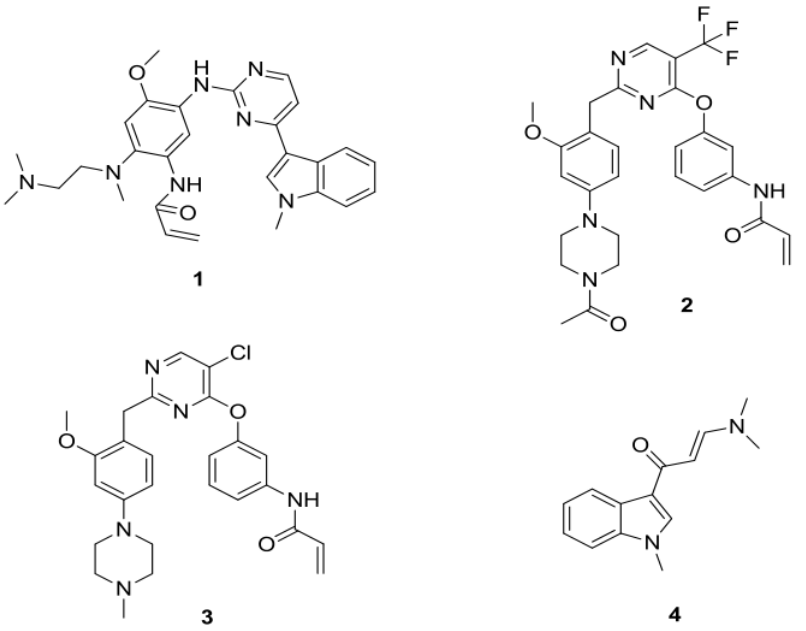
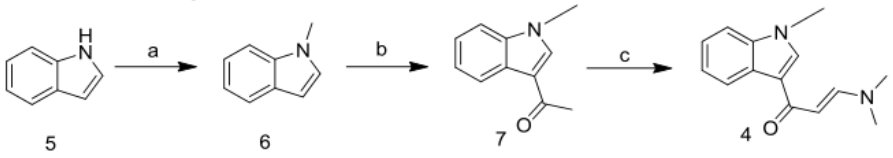


Fig.1 Structures of some drugs or active compounds containing

Chemistry

The structures and the synthetic route were shown in Scheme 1.



Scheme1. The synthetic route of Compound 4

Reagents and conditions: (a) Tetrahydrofuran, methyl iodide, sodium hydride, ice bath; (b) Diethyl aluminum chloride, acetyl chloride, ice bath, nitrogen protection; (c) Nitrogen dimethyl acetal, microwave, 2 h.

Synthesis of 1-methyl-1*H*-indole (6)

1H-indole (0.5g, 0.0043mol) was dissolved in tetrahydrofuran (15 mL) first. Ice bath and sodium hydride (0.5 g, 0.021 mol) were slowly added under stirring, stirred at room temperature for 30 minutes, and then slowly dropped methyl iodide (1.5 g, 0.011 mol) in an ice bath, stirred at room temperature to complete consumption of the reactants. The combined reaction solution was dried under reduced pressure to recover most of the solvent extracted with water and dichloromethane (with an equal volume of solvent). 1-methyl-1*H*-indole (0.505 g, 0.0039mol) was obtained. Yield 90.7%. ^{1}H NMR (400 MHz, DMSO) δ 7.51 (d, 0H), 7.28 (d, 0H), 7.18 (d d, *J* = 8.7 Hz, 1H), 7.06 (d d, 0H), 6.84 (d d, 0H), 3.81 (d, 1H).

Synthesis of 1-(1-methyl-1*H*-indol-3-yl) Ethan-1-one (7)

Under nitrogen atmosphere with ice bath, 1-methyl-1*H*-indole (0.5 g, 0.0038 mol) was first dissolved in methylene chloride and then diethyl aluminum chloride (0.61g, 0.0051mol) was added. After stirring for 30 minutes, a mixed solution of acetyl

chloride0.23g, 0.0029mol) and dichloromethane (10 mL) were added. Then the reaction was completed, the mixture was extracted three times with aqueous alkali and dichloromethane, and the organic phase was evaporated to dryness and recrystallized from petroleum ether to give 1- (1-methyl-1H-indol-3-yl) ethan-1-one(0.52g, 0.003mol). Yield 78.79%. ^{1}H NMR (400 MHz, DMSO) δ 8.41 (s, 1H), 8.18 (d, 1H), 7.49 (d, 1H), 7.40 (t, 1H), 7.35 (t, 1H), 3.85 – 3.82 (m, 3H), 2.55 (s, 3H).

Synthesis of (*E*) -3- (dimethylamino) -1- (1 -methylindolin-3-yl) prop-2-en-1 –one (4)

After mixing 1-(1-methyl-lH-indol-3-yl)ethan-1-one(0.1 g, 0.006 mol))and *N*,*N*-Dimethylformamide dimethyl acetal (1.5 g, 0.0126 mol) , the mixture was microwaved (110℃, 150 PSA, 50 W) and stirred for two hours. After the reaction was completed, the mixture was extracted three times with a saturated solution of sodium bicarbonate and methylene chloride. The solvent was distilled off and recrystallized from ether to give (*E*)-3-(dimethylamino)-1-(1-methylindolin-3-yl) prop-2-en-1- one (0.08 g, 0.0003 mol). Yield 50%.^{1}HNMR (400 MHz DMSO) δ 8.99 (d, 1H), 8.42 (s, 1H), 8.04 (d, 1H), 7.45 (d, 1H), 7.36 (t, 1H), 7.29 (t, 1H), 5.45 (d, 1H), 3.81 (s, 3H), 2.85 (s, 6H).

Conclusion

In conclusion, compound 4 is an important intermediate for many anticancer drugs. (1*H*-indol-3-yl) prop-2-en-1-one is synthesized using 1*H*-indole as a starting material after two substitutions and one condensation reaction. The synthetic method of compound and the reactions conditions were optimized, the purity of the product was much higher.

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