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Design and Synthesis of Selective Cyclooxygenase-2 Inhibitors Derived from Thalidomide

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Abstract. Three series of compounds derives from thalidomide were designed and synthesized. Using commercial available material bromohydrocarbon to partly protect the 5-amino-2-thiolthadiazole, the protected thiadiazole derivatives were treated with phthalidomide. Dicarboximide derivatives were reduced in two different ways to give the target molecules.

Keywords: thalidomide, inhibitors of cuclooxygenase-2, derivatives, design, synthesis.

1. Introduction

Thalidomide was an efficient temperantia.The first used to treat gestation reaction of pregnant women[1].Because the molecular biology mechanism of thalidomide is still uncovered and its extensive bioactivity, the clinical and medical research to thalidomide is on going. In 1965, Sheskin treated the ENL with thalidomide and get ideal effect[2]. In 1991, Sampaio reported that thalidomide can inhibit the level of tranf-a.[3]. In 1994, D'Amato firstly reported thalidomide effectly inhibit the form of new vessels via bFGF[4]. Kenyon[5] and Kruse[6] discover that thalidmide can also inhibit the form of new vessels via VEGF induction. In 1998, thalidomide was approved to treat the ENL in the clinical use by FDA[7]. Takumi Ito identified the binding target of thalidomide in 2010[8], this would be the milestone of drug discover of thalidomide.

Based on the structure-activity relationship research of thalidomide covered in the literatures,we maintain the active sites of inhibiting cox-2 in the thalidomide and desert the structure units with no cox-2 inhibiting activity. The glutarimide was displaced with 5-amino-2-thiolthiadiazole that is a excellent and effective selective cyclooxygenase-2 inhibitor. We also investigated the relationship between the magnitude of the side chain and the bioactivity of the target molecules. And the reduction in the phthalidmide was also carried out to inspect the influence to the activity of inhibiting the cyclooxygenase-2. In conclusion, we aim to discover a new type of cox-2 inhibitors through structural modification based on thalidomide.

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2. Materials and methods

Melting Points(uncorrected) were determined on a XT-4 binocular microscope melting point instrument. ^{1}HNMR and^{13}CNMR spectra were recorded at 400 and 100 MHz, and chemical shifts are given in δ units relative to the tetramethylsilane (TMS) signal as an internal reference in CDC_{l3}.Analytical TLC of all reactions was performed on silica gel GF-254 plates.Column chromatography was performed using silica gel(100-200 mesh).The main reagents like phthalic, anhydride, $NaBH_4$, Zinc, CS_2, bromobenzyl, etc were obtained from commercial sources and used without further purification. Solvents for chromato-graphy are of technical grade and were distilled before use.

Scheme1: The strategy of synthesis of the cyclooxygenase-2 inhibitors derivatives of thalidomide.

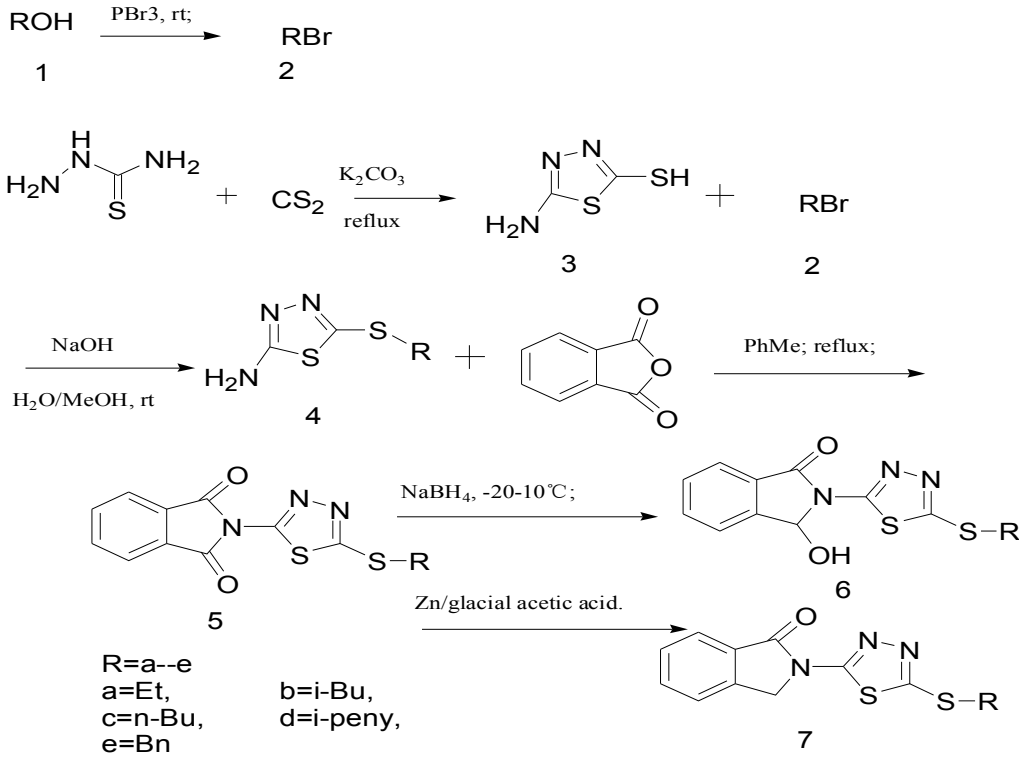

Fig.1: The strategy of synthesis of the cyclooxygenase-2 inhibitors derivatives of thalidomide.

3. Results

In conclusion: we have successfully synthesized two series of N-thiadiazole phthalimide derivatives of thalidomide:6a-e and 7a-c, by using partly protected thiaidazole and phthalidomide. These new compounds have potent selective cycloxygenase-2 inhibiting activity. The following is the^{1}HNMR and ^{13}CNMR data of the target compounds. Synthesis of 7a-c and 6b-e.7a of compound: White needle crystallize. mp:134-135 ℃ .59.3 % .^{1}HNMR(400MHz,$CDCl_3$)δ1.418-1.414 (t,3H,CH_3),δ3.215-3.270(q,2H,SCH_2), δ4.829(s,2H,CH_2),δ7.459-7.497(m,2H,Ar-H),δ7.541-7.582(m,1H,Ar-H),δ7.976-7.999(d,1H.Ar-H).^{13}CNMR(100 MHz,DMSO-d6)δ167.063,159.127,141.753,131.557,128.788,128.003,127.057,61.07,28.301,15.001.

7b of compound: Light yellow needle crystallize. mp:174-176℃.51.0%.^{1}HNMR(400MHz,$CDCl_3$)δ1.061-1.078(d,6H,CH_3), δ2.001-2.068(m,1H,CH) δ3.130-3.147(d,2H,CH_2),δ7.468-7.503(m,2H,Ar-H), δ7.549-7.585 (m,1H,Ar-H), δ7.970-7.993(m,1H,Ar-H).

7c of Compound: White needle crystallize.mp:128-130 ℃ .42.0 % . ^{1}HNMR(400MHz,$CDCl_3$),δ0.942-0.978(t,3H,CH_3),δ1.440-1.533(m,2H,CH_2), δ3.210-3.247(t,2H,SCH_2), δ7.466-7.496(m,2H,Ar-H), δ7.542-7.579(m,1H,Ar-H),δ7.976-7.999(m,1H,Ar-H).

6a of Compound: White needle crystallize.mp:128-130 ℃ .84.3 % . ^{1}HNMR(400MHz,$CDCl_3$) δ1.469-1.505(t,3H,CH_3), δ3.290-3.345(q,2H,CH_2), δ5.214-5.223(d,1H,CH),δ6.785-6.795(d,1H,OH), δ7.761-7.765

(m,1H,Ar-H), δ7.774-7.772(m,2H,Ar-H), δ7.939-7.958(d,1H,Ar-H) .^{13}C NMR(100MHz,DMSO-d6) δ:167.080,159.150,143.540,141.770,131.585,128.828,128.049,127.078,61.122,28.337,15.021.

6b of Compound: White needle crystallize mp:132-133℃.86.1%.^{1}HNMR(400MHz,$CDCl_3$)δ1.083-1.100 (d,6H,CH3),δ2.058-2.125(m,1H,CH), δ3.206-3.322(d,2H,CH_2), δ5.121-5.149(m,1H,CH),δ6.781-6.790 (d,1H, OH) δ7.623-7.663(m,1H,Ar-H),δ7.763-7.778(m,1H,Ar-H), δ7.947-7.956(d,1H,Ar-H).

6c of Compound: White needle crystallize. mp:140-142℃.92.0%.^{1}HNMR(400MHz,$CDCl_3$)δ0.946-0.983 (t,3H,CH_3),δ1.474-1.530(q,2H,CH_2),δ1.766-1.841(m,2H,CH_2), δ3.283-3.320(t,2H,CH_2), δ5.176-5.185(d,1H,CH), δ6.781-6.790(d,1H,OH), δ7.618-7.658(m,1H,Ar-H),δ7.758-7.773(m,2H,Ar-H), δ7.941-7.960(d,1H,Ar-H).

6d of Compound: White flocculate crystallize. mp:178-180℃.77.0%.^{1}HNMR(400MHz,$CDCl_3$)δ0.955-0.971(d,6H,CH_3),δ1.673-1.697(m,2H,CH_2),δ1.706-1.790(m,1H,CH), δ3.290-3.328(t,2H,CH_2),δ5.130-5.136(d, 1H,CH),δ6.780-6.789(d,1H,OH),δ7.618-7.658(m,1HAr-H),δ7.758-7.773(m,2H,Ar-H) δ7.941-7.961(d,1H,Ar-H).

6e of Compound:White needle crystallize. mp:180-181℃.87.0%.^{1}HNMR(400MHz,$CDCl_3$)δ4.484-4.554 (t,2H,CH_2),δ5.170-5.179(d,1H,CH),δ6.777-6.785(d,1H,OH), δ7.289-7.358(m,3H,Ar-H), δ7.416-7.434(d,1H, Ar-H), δ7.609-7.649(m,1H,Ar-H)δ7.734-7.766(m,2H,Ar-H),7.928-7.947(d,1H,Ar-H).

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