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An efficient one pot synthesis of Dibenzo [b, f] [1, 4] thiazepin-11[10H]-one: A key intermediate for synthesis of Quetiapine an antipsychotic drug

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ABSTRACT

An efficient one pot synthetic pathway is described for Dibenzo [b, f] [1, 4] thiazepin-11[10H]-one, a key intermediate in the synthesis of Quetiapine. The procedure starts from 1-chloro-2-nitrobenzene and involves five simple insitu steps in one pot to give Dibenzo [b, f] [1, 4] thiazepin-11[10H]-one in 70% overall yield with >99% purity. © 2015 Trade Science Inc. - INDIA

KEYWORDS

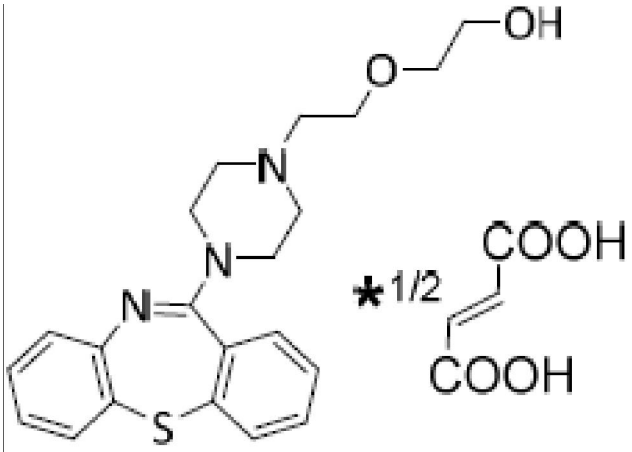
Dibenzothiazepin;
One pot synthesis;
Quetiapine;
Schizophrenia.

INTRODUCTION

Quetiapine hemifumarate (1)[1-2] is chemically known as hemifumarate salt of 2-(2-(4-dibenzo [b,f] [1, 4] thiazepin-11-yl) piperazin-1-yl-ethoxy) ethanol (**1**) which is marketed by AstraZeneca under the trade name 'seroquel'. Quetiapine is clinically effective for the treatment of Schizophrenia.

Dibenzo [b, f] [1, 4] thiazepin-11[10H]-one which is a key intermediate for preparation of Quetiapine is represented by the Formula **2**.

From the literature precedents two approaches were reported, one is linear approach [3-4] and another one is convergent approach [5-8], for the preparation of compound (**1**) from compound **(2)** as illustrated in Figure 1. Common intermediate **(3)** was isolated in both meth-



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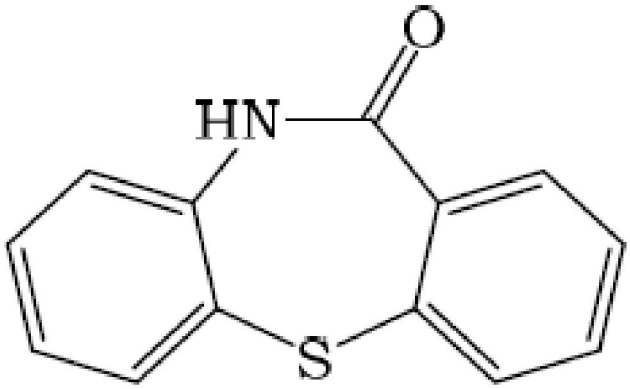

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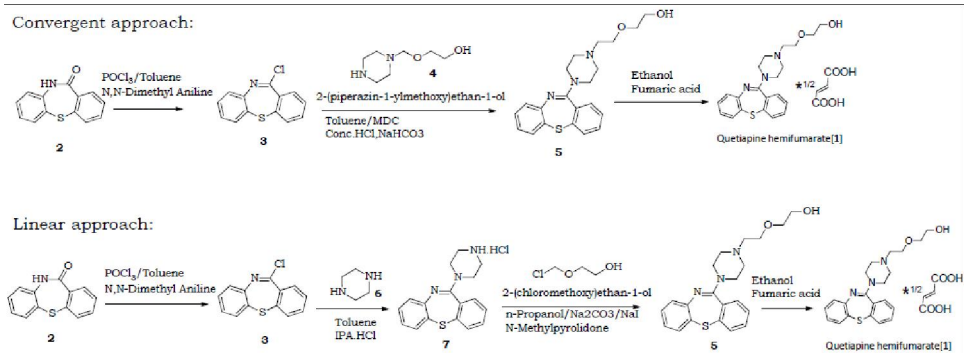


Figure 1 : General synthetic routes to synthesis quetiapine hemifumarate (1)

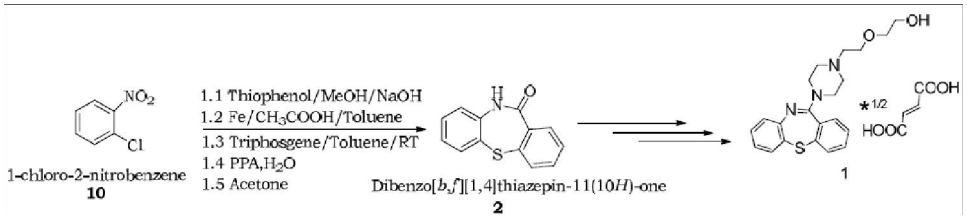


Figure 2 : One pot synthetic route to synthesis Dibenzo [b,f][1,4] thiazepin-11 [10H]-one (2)

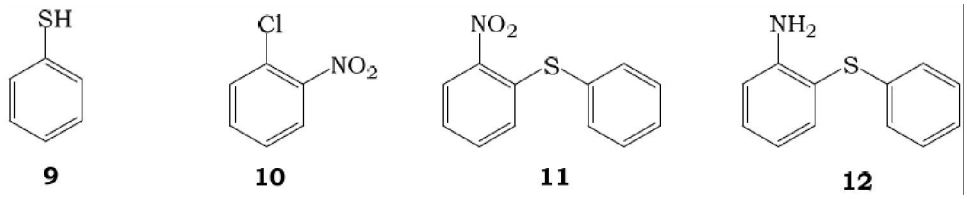
ods by reacting compound **(1)** with $POCl_3$ in the presence of N, N dimethylaniline at reflux temperature in organic solvent. In convergent approach condensation of **3** with 2-(2-piperazin-1- ylethoxy)ethanol (**4**) under reflux in organic solvent followed by workup provided quetiapine base (**5**) as a viscous oil, which was further treated with fumaric acid in ethanol to obtained compound **(1).** In linear synthesis compound **(3)** reacts with Piperzine **(6)** to obtain **7** that was further reacted with 2-chloroethoxyethanol (**8**) to yield compound **(5)**, as a viscous oil, which was further treated with fumaric acid in ethanol to furnish compound **(1).**

RESULTS AND DISCUSSION

A plethora of synthetic routes for the preparation of compound **(2)**. They were mainly starting from, 2-aminobenzenethiol[8-10], 2-(phenylthio)aniline[11-12],Thiosalicycicacid[13-16],2,2'-Dithiosalicylic acid[16] and 9H-thioxanthen-9-one[17].

The reported synthetic methods from literature for the synthesis of Dibenzo [b, f] [1, 4] thiazepin-11[10H]-one (**2**) involve multistep synthesis with isolation of intermediates and repeated exchange of solvents. This is a disadvantage both from an ecological and economical point of view. Further, the reported schemes have various disadvantages such as low yield, use of high temperature and use of hazardous compounds. These disadvantages are unfavorable for the industrial scale synthesis. Thus there is an unmet need for an efficient method for synthesis of Dibenzo [b, f] [1, 4] thiazepin-11[10H]-one (**2**). Herein, we report our efforts to develop an efficient synthesis to access compound **(2)** by utilizing one pot synthesis as illustrated in Figure 2 from commercially cheap 1-chloro-2-nitrobenzene.

The present synthesis provides simple one-pot process for the preparation of Dibenzo [b, f][1, 4] thiazepin-11[10H]-one of the compound **(2)** which process overcomes the shortcomings of the prior art processes by reaction of thiophenol of Compound **(9)** with 1-chloro-2-nitrobenzene of compound **(10)** in the presence of base to yield (2-nitrophenyl)(phenyl)sulfane of Compound **(11)** which on *in situ* reduction with iron powder in the presence of acetic acid affords 2-(phenylthio)-aniline of compound **(12)**, which on further *in situ* re-



9 **10** **11** **12**

acts with triphosgene followed by cyclization in the presence or absence of an organic solvent, to afford compound of formula **2**.

CONCLUSIONS

In summary, a simple, convenient one pot synthetic method has been developed for the preparation of Dibenzo [b, f] [1, 4] thiazepin-11[10H]-one utilizing easily accessible and inexpensive starting materials. This synthetic approach includes some important aspects such as high yields and mild reaction conditions, which make this synthetic protocol a useful and an attractive procedure for the industrial synthesis of Dibenzo [b, f] [1, 4] thiazepin-11[10H]-one thus producing block buster antipsychotic drug Quetiapine.

EXPERIMENTAL SECTION

Genearl: Reagents and solvents were obtained from commercial sources and used without further purification. All melting points were taken in open capillaries and are uncorrected. Thin-layer chromatography (TLC, on aluminum plates coated with silica gel 60 F254, 0.25 mm thickness, Merck) was used for monitoring the progress of all reactions, The 1H NMR, 13C NMR,spectra were recorded on a Bruker (Avance) 400 MHz NMR instrument using TMS as internal standard and $CDCl_3$ as solvent. Chemical shifts are given in parts per million (ä scale) and the coupling constants are given in Hertz. Mass spectra (70 eV) were recorded on a HP-5989A liquid chromatography–mass spectrometry (LC-MS) spectrometer.

Synthesis of Dibenzo [b, f] [1, 4] thiazepin-11[10H]-one (2)

Thiophenol (49.5 mL) and methanol (75 mL) were charged in a round bottom flask, at 25-30°C, stirred for about 30 minutes. To this reaction mass, aqueous solution of sodium hydroxide (19.35 g in 49.5 mL of water) was added and the mixture was maintained for 30 minutes. Then *o*-chloronitrobenzene (75 g) and methanol (150 mL) were added to the above reaction mixture and it was further maintained for 30-60 minutes. The reaction mass was then heated to reflux and maintained at same for about 3-4 hours, at which completion of the reaction was monitored by TLC. After completion of reaction, the temperature of the reaction mass was decreased to 50°C followed by addition of methanol (150 mL) and acetic acid (195 mL). The temperature of the reaction mass was raised to 58-60°C followed by sequential addition of iron powder (6 x 14.6 g) at 55-60°C (after addition of each lot of iron powder, the reaction mass was stirred for 30 minutes.). On complete addition of iron powder, the reaction mass was maintained at reflux temperature for 1-2 hours and completion of the reaction was monitored by TLC. After completion of reaction, the methanol from the reaction mass was distilled off completely under vacuum at below 60°C. Then, toluene (600 mL) was charged to the above crude compound and mixture was stirred for 1 hour at 60°C followed by cooling to 20-30°C and filtered through hyflow bed. The bed was washed with toluene (150 mL), filtrates were combined and sequentially washed with water (375 mL), 10% aqueous solution of sodium bicarbonate (30 g in 300 mL of water) followed by separation of layers. The organic layer thus obtained was further washed with water (375 mL), dried with sodium sulfate (15 g) and used for further reaction. In a separate flask, triphosgene (84.6 g) was dissolved in toluene (375 mL) and the mixture was cooled to -10 to 0°C followed by slow addition of earlier obtained organic layer (toluene) at the same temperature over a period of about 3 hours. On complete addition, the temperature of the reaction mass was raised to 20-30°C and mixture was maintained at the same temperature for about 4 hours, completion of the reaction was monitored by TLC. After completion of reaction, 10% aqueous solution of sodium bicarbonate (45 g in 450 mL of water) was added to reaction mass and stirred for 2 hours. The organic layer was separated and washed with water (375 mL) followed by separation and distillation of solvent from the organic layer under vacuum at below 65°C. The traces of toluene were chased with acetone (37.5 mL) at below 65°C followed by addition of polyphosphoric acid (373.5 g). The temperature of reaction mass was raised to 100-105°C and maintained for 6 hours at the same temperature for completion of reaction as monitored by TLC. The temperature of the reaction mass was lowered to 80-90°C followed by slow addition of pre-cooled water (1800 mL) at a rate of 600 mL per hour at the same tempera-

ture. The reaction mass was then transferred into another flask containing water (825 mL) at 85°C, then the mixture was cooled to 25-35°C and maintained at same for 30-60 minutes. The solid obtained was isolated by filtration. To the solid obtained, water (1800 mL) was added and mixture was stirred for 60-90 minutes followed by filtration and washing of solid with water (150 mL). The wet compound was taken up in acetone (225 mL), mixture was stirred for 1 hour followed by filtration, washing of solid with acetone (75 mL) and subsequent drying of solid at 55-60°C to afford the desired compound in 70%yield. Melting range: 259-260°C. MS (m/z): 228.2 (M+H). ^{1}H NMR (400MHz, $CDCl_3$) 7.1 (t, J = 7.5 Hz, 4H), 7.21(d, J = 7.8 Hz, 1H), 7.31-7.36 (m, 1H), 7.41-7.55 (m, 1H), 7-65-7.67 (m, 1H), 10.7 (br s, 1H). ^{13}C NMR (100MHz, CDCl3), 122.2, 126.0, 128.3, 129.4, 130.2, 131.8, 131.9, 132.2, 133.0, 137.0, 137.2, 139.2, 169.4.

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