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A facile electrochemical synthesis of suvorexant

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ABSTRACT

A facile, scalable electrochemical method to prepare Suvorexant has been developed. Two different electrochemical routes explored. The route with the high yield and less step taken forward.

Introduction

Suvorexant also known as MK-405 [1] is a dual orexin receptor antagonist for treating insomnia [2,3], improved sleep onset and maintenance [4]. Suvorexant has an appreciative tolerability, low potential for addiction and limited side effects thus having an edge over other medicines prescribed for sleep disorder. Given its global acceptance, many groups have developed different synthetic routes (Scheme 1). While Wacharasindhu *et al* used 5-chloro-2-mercapto benzoxazole coupled with 2-amino ethanol under microwave condition [5], irradiation with white light and Rose Bengal as photo catalyst [6] is also reported. This intermediate on further processing afforded Suvorexant. Cox [7] and Chen [8] had developed a process where the **5** was prepared and coupled with 2,5 dichloro benzoxazole at the final step to get Suvoraxant. To the best of our knowledge, to date none have reported an electrochemical methodology to prepare Suvorexant. However, Gao *et al* [9] and Ackermann *et al* [10] have previously reported the electrochemical C—H amination step in the past, but none have utilised that for the synthesis of suvorexant.

Electrochemisty as a technique in organic synthesis has started to gain wide acceptance due to its width of application [11–15]. This methodology offers the advantages of being mostly clean, green, eliminating formation of side products, good yields, and ability to control the reaction at the flick of the switch apart from reducing the bio-burden of effluent treatment. Most electrochemical reactions are carried out at room temperature with few exceptions where moderate temperature needed for conversion. In continuation to our earlier work [16], we have developed an electrochemical method to synthesise Suvorexant in good yields. We explored two routes. In our first route, we have electrochemically coupled 5-chloro benzoxazole (**7**) with *tert*-butyl (R)-7-methyl-1,4-diazepane-1-carboxylate (**6**) in the first step, which was used further to prepare **14**. In the second route, we prepared **5** and electrochemically coupled with **7** in the final step to form **14**. Once we identified the advantages and the overall yields of both the routes, the best possible route used further to prepare **14** on scale.

Results and discussion

The initial trials were carried out with **7** and **6** as starting materials using TBAI as a supporting electrolyte with catalytic amount of acetic acid in dry acetonitrile as a solvent using carbon rod as anode and an aluminium wire as the cathode. The reaction was complete in 3 h and **8** isolated in 95% yield. However, a column purification needed to remove the Tetrabutylammonium part from the crude material. The insolubility of the electrolytes in water as well as organic phases needed the crude material to be treated with resin [17] to ensure removal of TBAI. With an aim to easily remove the electrolytes by aqueous workup, we screened a few water-soluble electrolytes (Table 1). Using Ammonium Iodide and Ammonium Bromide, we achieved 12% and 17% conversion respectively while with Ammonium perchlorate we observed 23% conversion. We did not observed the formation of **8** when 5% aqueous sodium bromide solution was used.

The use of acetic acid to open the benzoxazole ring into O-hydroxyamidine derivative (**A**) [18,19] is known. The opening of

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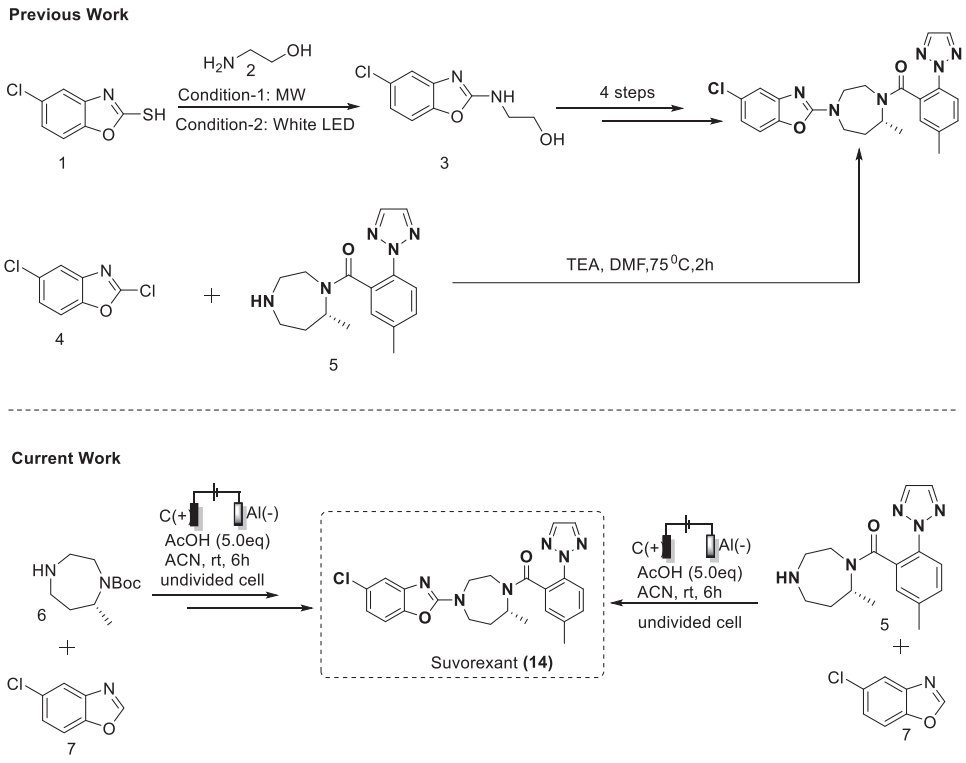


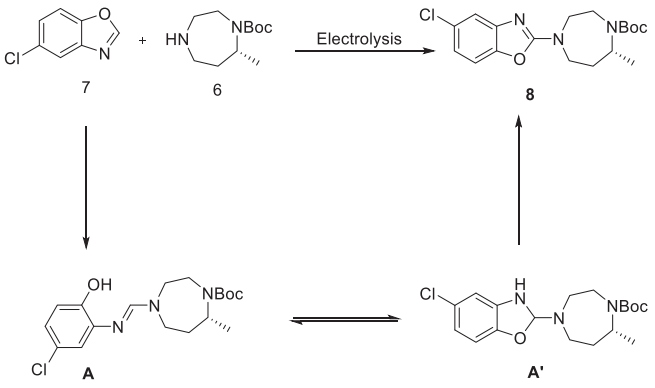
Scheme 1. Synthesis of Suvorexant through various routes.

Table 1
Screening of conditions for water-soluble electrolytes.

Entry	Electrolyte	% Conversion	Time
1	Ammonium Iodide	17	6 h
2	Ammonium Bromide	12	6 h
3	Ammonium perchlorate	23	6 h
4	5% aqueous Sodium Bromide	ND*	6 h
5	Acetic Acid	93.5	6 h

* ND = Not Detected.

the benzoxazole system in the presence of acetic acid to form O-hydroxyamidine derivative (**A**) and its oxidation at the anode resulted in **8** (Scheme 2). The formation of O-hydroxyamidine derivative (**A**) before moving to the anodic oxidation was observed in LCMS data. In one of the trials, we used acetic acid as an electrolyte and observed the initiation of the reaction within one hour and completion of the reaction within 6 h resulting in an isolated yield of 93.5% of **8**. Although the reaction took longer, purification was not needed in this step. We also observed that the presence of acetic acid was essential, as the reaction was unsuccessful in its absence. The mechanistic role of acetic acid in the reaction is well demonstrated by Ackermann *et al* [10]. A negative reaction performed under similar conditions in the absence of electric current confirmed no product formation.

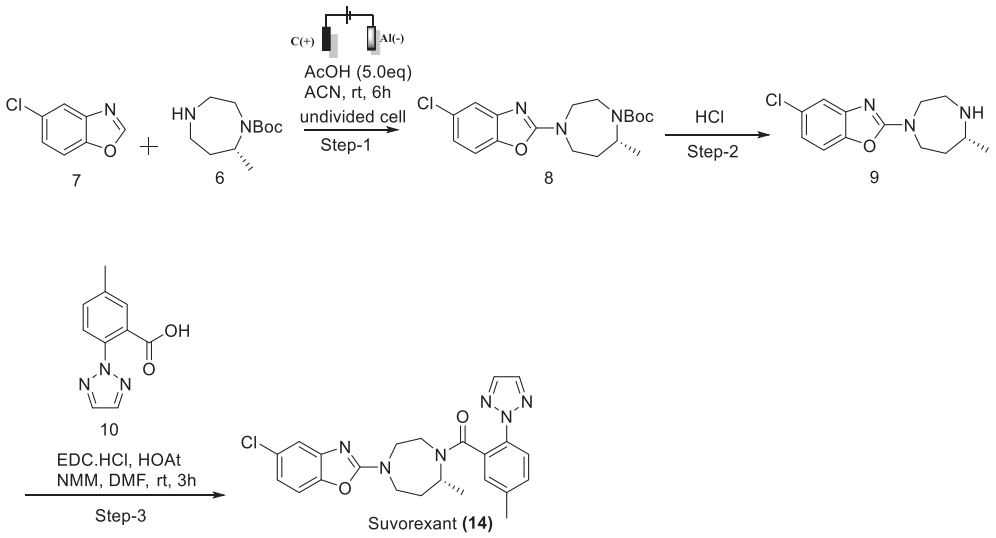


Scheme 2. Plausible electrochemical synthesis of Int-8.

Successful electrochemical coupling of **6** and **7** in the presence of acetic acid resulted in a key intermediate 8 that was used to synthesise Suvorexant (Route-1, Scheme 3). Removal of the Boc group by 4 M HCl in Dioxane followed by trituration of the crude with diethyl ether resulted in **9** as its hydrochloride salt in 96% yield. Coupling of **9** with **10** led to Suvorexant in 91% yield. Thus starting with 5-chlorobenzo[*d*]oxazole (**7**) we prepared Suvorexant in three steps with overall yield of 81.1%.

The scalability of the electrochemical conversion was carried out on 1 g, 5 g and 10 g scale and **8** was isolated in similar yields (Table 2). All the electrochemical transformation carried out in an electrochemical reactor prepared from a mobile phone charger, which had an output current density of 0.35A.cm^{-2}. The wire from the mobile phone charger was connected to the electrodes through alligator clips and constant current passed for 3–6 h for complete conversion to product.

Scheme 4 shows the alternate route where **5** was prepared in four steps. Electrochemical coupling of **5** with **7** using a carbon rod as anode and an aluminium rod as the cathode resulted in synthesis of **14** with overall 35.6% yield. Protection of **6** with benzyl chloroformate gave **11** in 86% yield. Removal of the Boc group in **11** by 4 M HCl in Dioxane gave **12** in 87.7% yield as its hydrochloride salt. Coupling of **12** with the acid counterpart resulted in **13** in 78%-isolated yield, which was purified by column chromatography before using it in the next step. Removal of the Cbz group in **13**



Scheme 3. Three step electrochemical synthesis of Suvorexant (Route-1). [a]*Reaction Conditions:* Step-1: Int-7, Int-6, Undivided cell, C anode/Al cathode, HOAc, Acetonitrile, rt, 6 h, 93.5%, Step-2: HCl in Dioxane, rt, 3 h, 96%, Step-3: Int-10, EDC.HCl, HOAt, *N*-Methyl Morpholine, DMF, rt, 3 h, 91%.

Table 2
Summary of Scale up reaction.

Entry	I Quantity of **7**	Quantity of **6**	Isolated Yield of **8**
1	153 mg, 0.99 mmol	213 mg, 0.99 mmol	340 mg, 93%
2	1.0 g, 6.5 mmol	1.39 g, 6.5 mmol	2.18 g, 91.6%
3	5.0 g, 32.5 mmol	6.95 g, 32.5 mmol	11.1 g, 93.2%
4	10 g, 65 mmol	13.9 g, 65 mmol	21.78 g, 91.8%

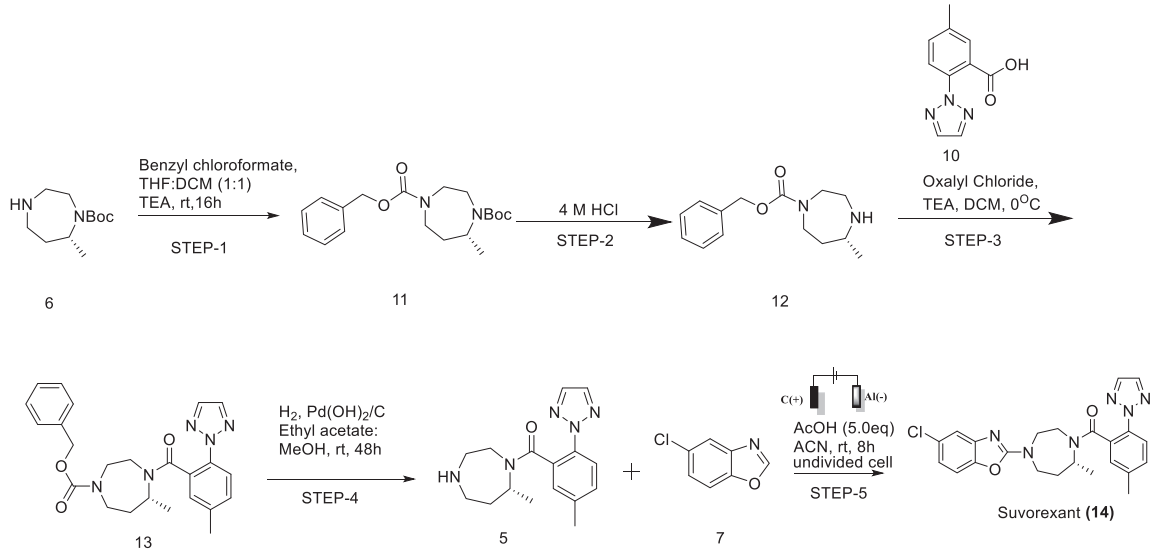
gave **5** which was used directly for the final step. The final electrochemical step resulted in isolating Suvorexant in 64.66% yield.

Conventional coupling of **7** with N-Boc-ethylenediamine (**15**) through electrochemistry was unsuccessful, very complex mixture was observed on TLC and desired product was not isolated. However, we felt if we could prepare *tert*-butyl (2-((3-oxobutyl) amino)ethyl)carbamate (**17**) by any method then this sidechain which has a free secondary amine could be electrochemically coupled with **7** followed by steps of the conventional route (Scheme 5).

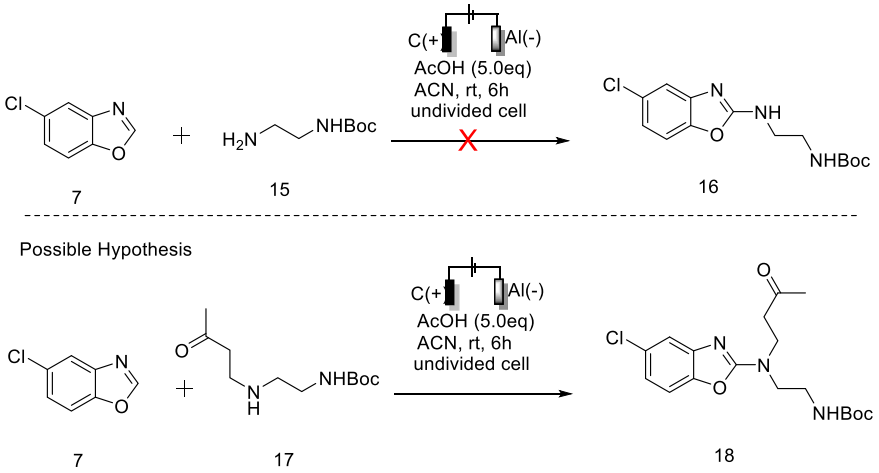
A comparison of both routes is shown in Table 3. Clearly, Route-1 offers distinct advantages compared to route-2 in terms of number of steps, yields and purifications. Based on the insights we chose Route-1 to prepare **14** on a 10 g scale.

Conclusion

In conclusion, we have demonstrated a clean, scalable and high yielding electrochemical method to prepare Suvorexant. Electrochemical coupling of **7** and **6** took 6 h and then the crude taken forward for subsequent steps. This improved methodology reduces the time required to synthesise Suvorexant.



Scheme 4. Electrochemical synthesis of Suvorexant (Route-2). [a]*Reaction Conditions:* Step-1: Int-6,Benzyl Chloroformate, THF: DCM (1:1), Triethylamine, rt, 16 h, 86%; Step-2: HCl in Dioxane, rt, 3 h, 87.7%, Step-3:Int-10, $(COCl)_2$, TEA, DCM, rt, 3 h, 78%,Step-4: $Pd(OH)_2$, MeOH, rt, 48 h, Step-5: Undivided cell, C anode/Al cathode, HOAc, Acetonitrile, rt, 8 h, 64.66%.



Scheme 5. Exploring alternate routes to prepare Suvorexant.

Table 3
Comparative study of both routes.

Parameters of Comparison	Route-1	Route-2
Number of Steps	3	5
Overall yield (based on Int-6)	81.5%	35.6%
Electrochemical step	First Step	Final step
Yield of the electrochemical step	91%	64.66%
Number of purification involved	1	3
Time taken (hours) for synthesis (mg scale)	3	8

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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