Synthesis of thiophene derivatives: Potential new inhibitors of histidine kinases

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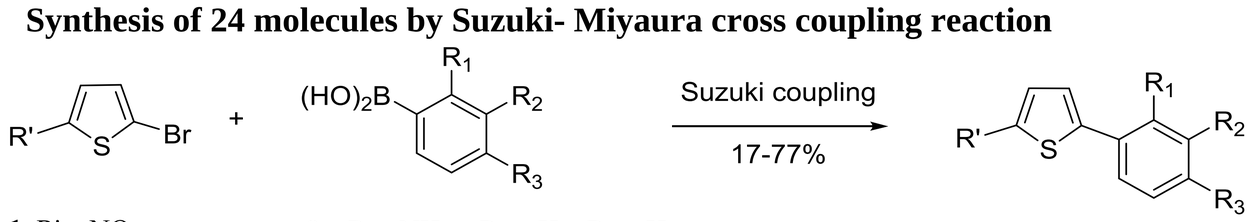
INTRODUCTION

Nowadays, infections caused by multidrug-resistant bacteria represent one of the biggest challenges in the medical field and there is an urgent need to develop efficient and well tolerated antibacterials targeting unique cellular processes. Two-component signal transduction systems (TCS) are widely used for bacteria to translate an external signal into a cellular response.[1] They are ubiquitous in bacteria, absent in mammals and are integrated into various pathogenic pathways.[1,2] In order to attenuate these signaling pathways, we aimed at targeting the TCS signal transducer histidine kinase by focusing on their highly conserved ATP-binding domain.[3] Preliminary modeling work carried out in our laboratory led to a serie of thiophene derivatives. Twenty-four new molecules were synthesized and evaluated *in vitro* on bacterial histidine kinases PhoR, ResE and WalK and also as adjuvant to assess their ability to restore the antibacterial activity of existent antibiotics. We identify eight compounds with significant inhibitory activity against these proteins. Nevertheless, only two compounds exhibited broad-spectrum antimicrobial activity and only one behaved as an adjuvant.[4] That is the reason why in order to improve the biological activity of the synthesized molecules, a new series of amino thiophene has been developed.

I- SYNTHESIS OF THE THIOPHENE SERIES

Synthesis of 24 molecules by Suzuki- Miyaura cross coupling reaction



1. R' = NO_2
2. R' = CH_3CO
3. R' = $NHCOCH_3$

2a. R_1 =NH_2 ; R_2 = H ; R_3 = H
2b. R_1 = H ; R_2 = NH_2 ; R_3 = H
2c. R_1 = H ; R_2 = H ; R_3 = NH_2
2d. R_1 = OH ; R_2 = H ; R_3 = H
2e. R_1 = H ; R_2 = OH ; R_3 = H
2f. R_1 = H ; R_2 = H ; R_3 = OH
2g. R_1 = OCH_3 ; R_2 = OCH_3 ; R_3 = H

Reagents and conditions : $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$, Na_2CO_3 or K_2CO_3 or Cs_2CO_3, Toluene/EtOH or 1,4-dioxane/H_2O or DMF/H_2O or DMF, 70-90°C.

Scheme 1: Synthesis of thiophenes derivatives

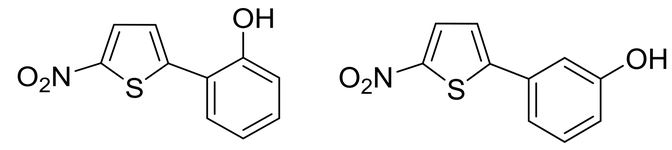
Characterisation: IR, ^1H and ^{13}C NMR, HPLC, UPLC and HRMS.

II- BIOLOGICAL RESULTS

Among the 24 synthezied molecules : **8 molecules are**

-Specific inhibitors of HK (WalK, PhoR and ResE)
-None inhibits eukaryotic serine/threonine kinase (IreK)
-None inhibits DNA gyrase
-None has hemolytical activity
-Only molecule **3** and **4** present antibacterial activity

⇒Only molecule **3** exhibits an **adjuvant activity** in association with antibiotics

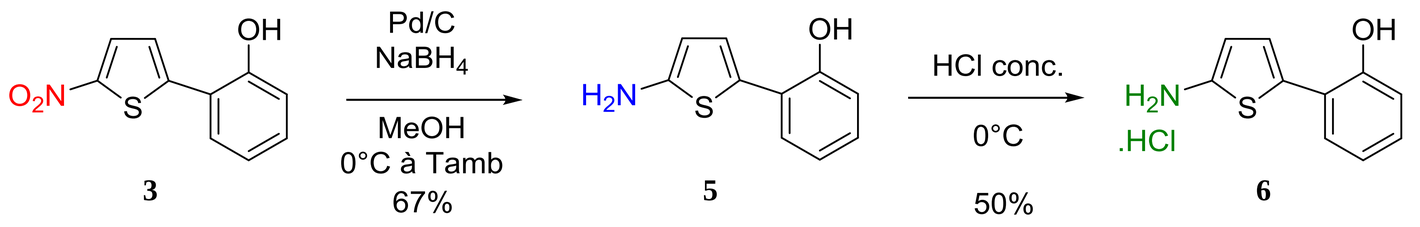


3 **4**

Figure 1: Structure of molecule **3** and **4**

III-SYNTHESIS OF AMINO THIOPHENE SERIES

Problematic reduction



3 **5** **6**

Solution

⇒**Two different strategies**

⇒**Only one condition reduces the nitro group** [5]

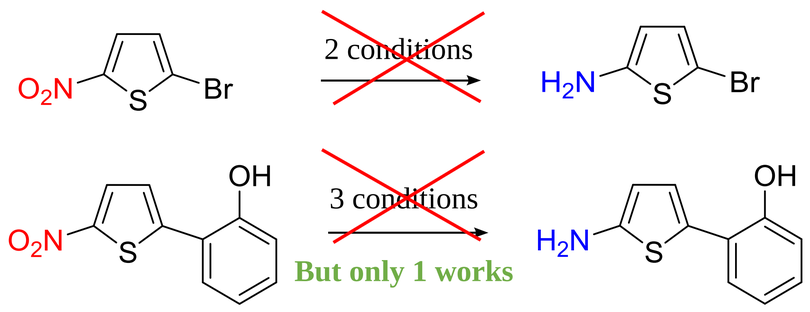


Figure 2: Different strategies for nitro reduction

Scheme 2: Synthesis of amino thiophene derivatives

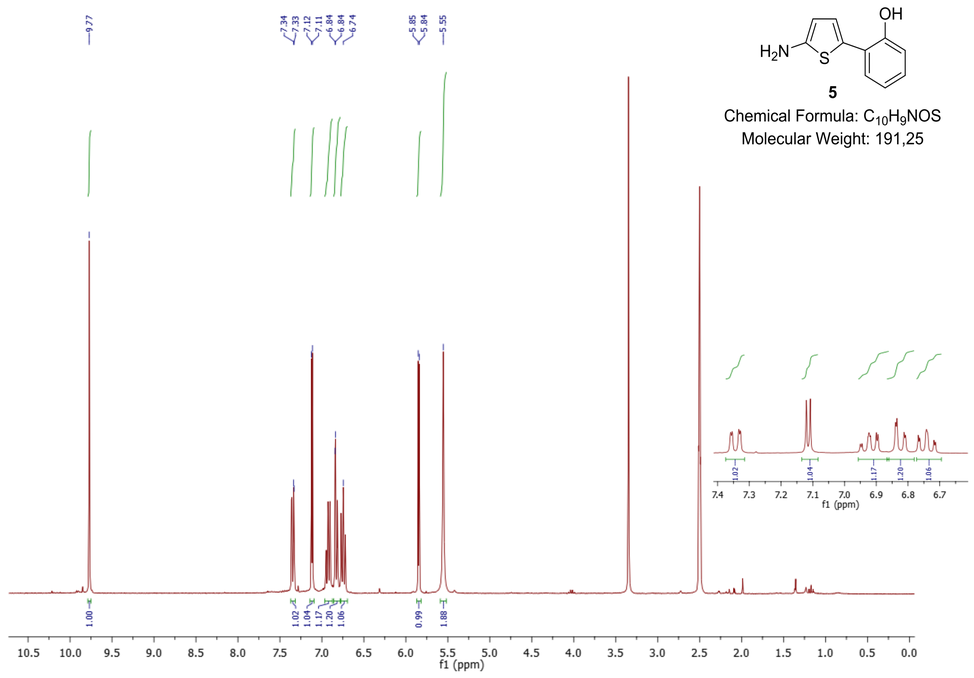


Figure 3: ^1H NMR spectra in DMSO-d_6 of molecule **5**

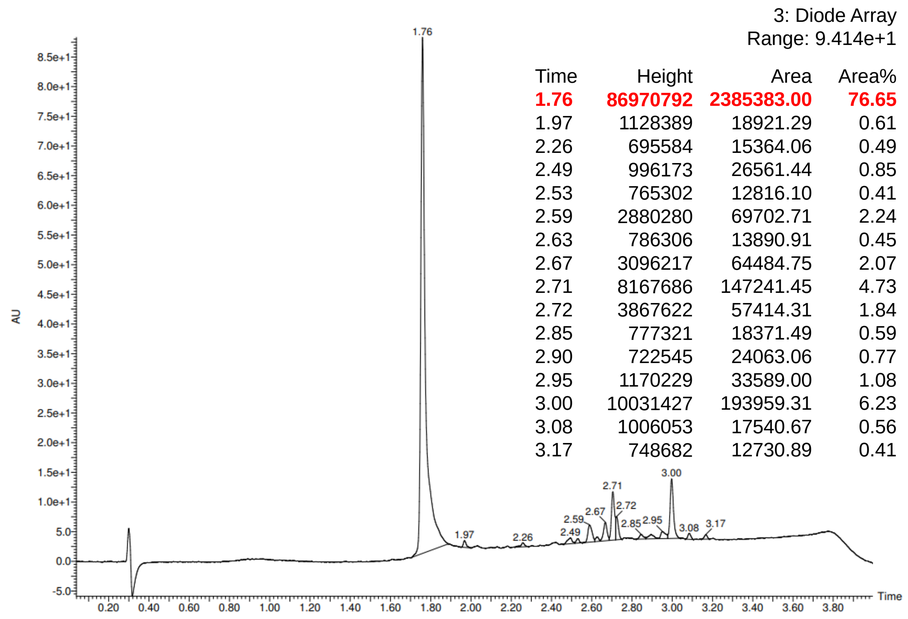
⇒**Confimation of the stucture of the desired product by NMR**

⇒**NRM spectra doesn't reveal any secondary product or impurities**

⇒**HRMS comfirms that molecule 5 have been synthezied**

⇒**UPLC shows that the purity of the compound is 76%**

Does the product degrade under UPLC conditions?



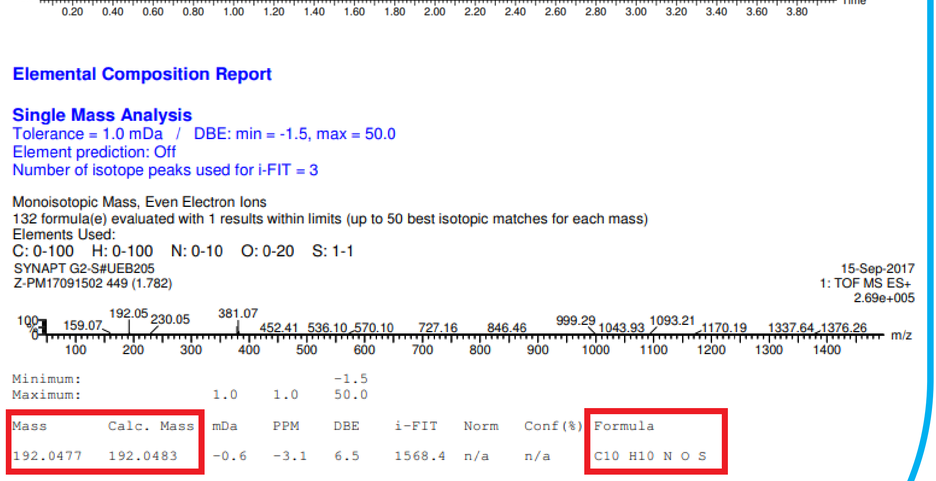


Figure 4: Ultra-performance liquid chromatography and High resolution mass spectra of molecule **5**

CONCLUSION

We have designed and synthesized a series of 24 molecules with thiophene ring by Suzuki-Miyaura coupling and have encouraging biological results. In order to improve previous results, the amino thiophene series was developed. Several conditions were tested to reduce nitro group. The structure was confirmed by NMR but UPLC showed us that the purity of the compound was 76%. Finally the corresponding salt was synthesized to stabilize the compound.

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