

Synthesis of thiophene derivatives: Potential new inhibitors of histidine kinases

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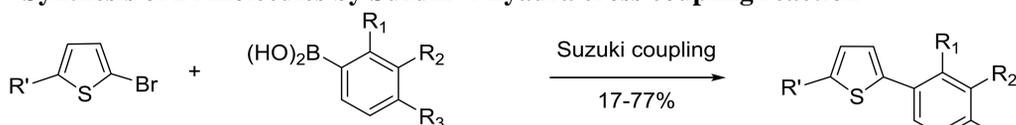
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INTRODUCTION

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 series 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' = NO₂
2. R' = CH₃CO
3. R' = NHCOCH₃
- 2a. R₁ = NH₂ ; R₂ = H ; R₃ = H
- 2b. R₁ = H ; R₂ = NH₂ ; R₃ = H
- 2c. R₁ = H ; R₂ = H ; R₃ = NH₂
- 2d. R₁ = OH ; R₂ = H ; R₃ = H
- 2e. R₁ = H ; R₂ = OH ; R₃ = H
- 2f. R₁ = H ; R₂ = H ; R₃ = OH
- 2g. R₁ = OCH₃ ; R₂ = OCH₃ ; R₃ = H

Reagents and conditions : Pd(PPh₃)₄ or PdCl₂(PPh₃)₂, Na₂CO₃ or K₂CO₃ or Cs₂CO₃, Toluene/EtOH or 1,4-dioxane/H₂O or DMF/H₂O or DMF, 70-90°C.

Scheme 1: Synthesis of thiophenes derivatives

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

II- BIOLOGICAL RESULTS

Among the 24 synthesized 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

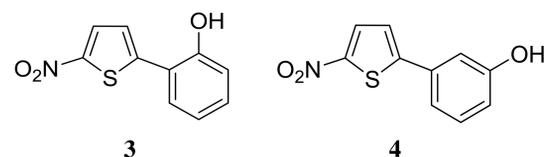
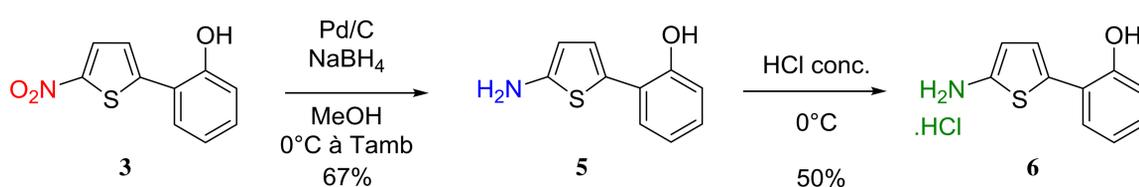


Figure 1: Structure of molecule 3 and 4

III-SYNTHESIS OF AMINO THIOPHENE SERIES

Problematic reduction



Scheme 2: Synthesis of amino thiophene derivatives

⇒ Two different strategies

⇒ Only one condition reduces the nitro group ⁵

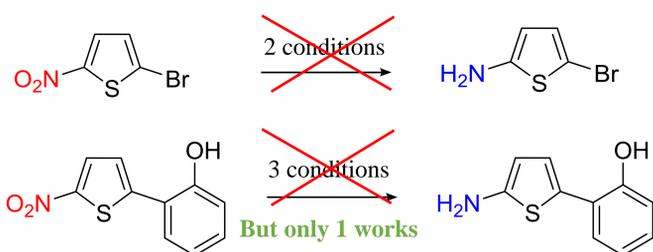


Figure 2: Different strategies for nitro reduction

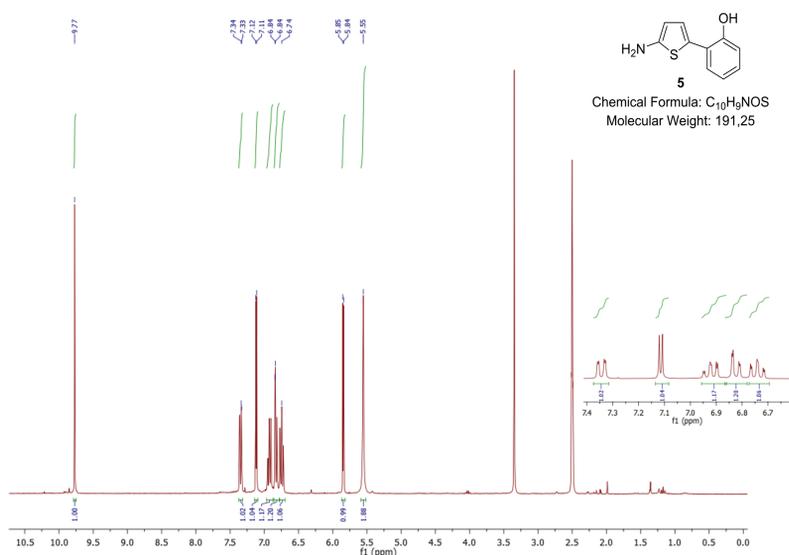


Figure 3: ¹H NMR spectra in DMSO-*d*₆ of molecule 5

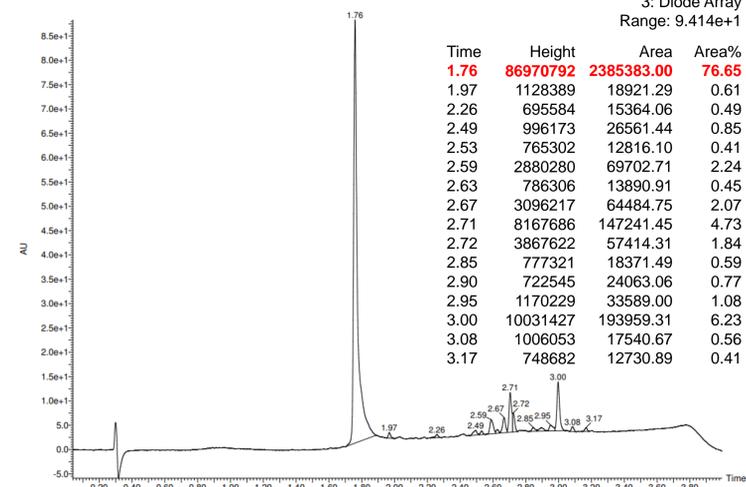
⇒ Confirmation of the structure of the desired product by NMR

⇒ NMR spectra doesn't reveal any secondary product or impurities

⇒ HRMS confirms that molecule 5 have been synthesized

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

Does the product degrade under UPLC conditions?



Elemental Composition Report

Single Mass Analysis
Tolerance = 1.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
132 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-100 H: 0-100 N: 0-10 O: 0-20 S: 1-1
SYNAPT G2-S#UEB205
Z-PM17091502.449 (1.782)

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
192.0477	192.0483	-0.6	-3.1	6.5	1568.4	n/a	n/a	C10 H10 N O S

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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