Synthesis and Citotoxicity Evaluation of 3-Cyano-2-amino-cycloalkyl[*b*]thiophene derivatives

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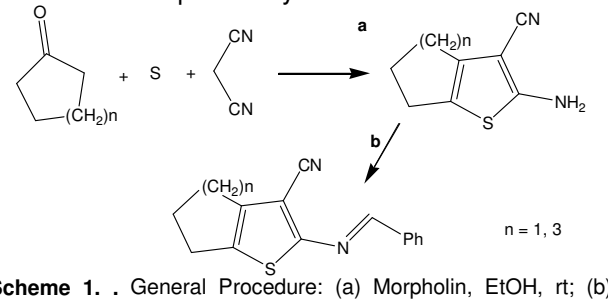
INTRODUCTION

The synthesis of new bioactive compounds requires preliminary testing to determine the toxicity and provide important indications of the feasibility of *in vivo* tests. The brine shrimp (*Artemia salina*) is a microcrustacean used as an animal model to determine the citotoxicity of synthetic compounds and natural products in lethality bioassays. This is a quickly and cheaply test with high correlation with other cytotoxicity bioassays. This study aims to synthesize and evaluate the citotoxicity of 2-amino-3-cyano-cycloalkyl[*b*]thiophene derivatives which possessed significant antifungal activity *in vitro*, through the *Artemia salina* lethality bioassay.

RESULTS AND DISCUSSION

Fourteen thiophene derivatives were synthesized in a two-step reaction, starting by the Gewald reaction[1] (generating two intermediates) followed by condensation of each one with aromatic aldehydes, generating the series 5CN and 7CN (Scheme 1). All compounds were characterized and their chemical structures were proved by ^{1}H NMR and CHOS.



Scheme 1. . General Procedure: (a) Morpholin, EtOH, rt; (b) ArCHO, AcOH, EtOH, rt.

All synthesized compounds were assayed for the lethality assay, which were conducted in accordance with the method proposed by Meyer[2]. Ten newly hatched nauplii were transferred to test tubes containing artificial sea water (Real Sea®) and from dilutions of stock solution of each one test compounds were prepared solutions at five different concentrations: 1000, 100, 10, 1 and 0.1 µg/ml. After 24 hours the percent deaths at each dose and control were determined. The tests were performed in quintuplicate. The LC_{50} (Table 1) were determined using the PROBIT analysis[3].

Table 1. Values of lethal concentration (LC_{50}) calculated by PROBIT analysis of thiophene derivatives

Radical	5CN	LC_{50}*	7CN	LC_{50}*
H	**01**	30,57	**01**	>1000
3,4-Cl	**02**	>1000	**02**	>1000
2,6-Cl	**03**	>1000	**03**	>1000
3,4,5-OCH_3	**04**	142,19	**04**	>1000
2,4-Cl	**05**	>1000	**05**	>1000
4-Cl	**06**	>1000	**06**	50,43
4-NO_2	**07**	>1000	**07**	71,03

* LC_{50} values in µg/ml

Only four compounds (5CN01, 5CN04, and 7CN06 7CN07) had LC_{50} less than the highest dose evaluated and could have their LC_{50} values determined. The LC_{50} values were respectively 30.57, 142.19, 50.43 and 71.03 µg/ml. All other compounds showed low or no cytotoxicity under the conditions tested (LC_{50} > 1000µg/ml).

CONCLUSION

The compounds were synthesized in excellent yields (55-99%). Tests for lethality to brine shrimp were able to evaluate the cytotoxicity of the compounds and demonstrated that the majority of tested compounds (71%) are non-toxic (LC_{50}> 1000).

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PIBIC/UEPB/CNPq PRPGP/UEPB CNPq

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