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Original Article

Novel and Efficient One-Pot Tandem Synthesis of Tryptanthrin Derivatives for Biological Activity

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ABSTRACT

In this study, the derivatives of tryptanthrin were prepared from three schemes. Those derivatives are characterized by NMR study. Reaction of 5-methyl-, 5-bromo-, and 5-iodoisatins with phosphoryl chloride gave the corresponding 2, 8-disubstituted indolo[2,1-b]quinazoline-6,12-diones in moderate yield. 5,7-Dichloroisatin failed to react with POCl3. Treatment of an equimolar mixture of isatin and 5-bromoisatin with POCl3 afforded indolo[2,1-b]-quinazoline-6,12-dione (tryptanthrin), 2,8-dibromoindolo[2,1-b]quinazoline-6,12-dione, and two isomeric monobromo-substituted tryptanthrin derivatives, the 2-bromo isomer prevailing.

KEYWORDS: Tryptanthrin, one-pot synthesis, 2-bromo acetophenone.

1. INTRODUCTION

Tryptanthrin is a natural product containing an indolo [2,1-b]quinazoline ring system isolated from the indigo plant *Strobilanthes cusia Kuntze* (Acanthaceae) and its relatives [7]. A number of biological activities have been reported for tryptanthrin or its analogues. These compounds, exhibit growth inhibition of Bacillus subtilis, permeabilized *Escherichia coli, methicillin resistant Staphylococcus aureus, dermatophytic fungal pathogens, Plasmodium falciparum, Leishmania donovani, Trypanosoma brucei,* and *Toxoplasma gondii* [8]. The direct C-H bond functionalization,

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particularly sp^3 C-H bond functionalization for the formation of C-C and C-N bonds has become an very imperative synthetic strategy.[1] C-H functionalization usually makes use of the metal catalyzed activation and consequent functionalization of sp^3 and sp^2 C-H bonds, which directly fix main functional groups to enhance the structural complexity of simply-prepared substrates [2]. In current years, great effort has been made toward the direct functionalization of C–H bond. However, most of these reactions need the use of costly Ru-, Rh-, Ir- and Pd-complexes as catalysts [3]. Recently, I_2-catalyzed C–H functionalization reactions have gained huge interest due to their cost efficiency, low toxicity, availability and broad functional group tolerance.[4] In this paper, an I_2-promoted sp^3 C-H functionalization for accessing tryptanthrin derivatives is illustrated.

Indole moiety is a privileged structural pattern in many biologically active and medicinally essential molecules. The indole built-in quinazolines have been well-known asimportant heterocycles in pharmaceutical areas and a building block for a huge number of structurally diverse alkaloids with a broad range of biological activities.[5] More specifically, the fused quinazolinones such as asperlicins, benzomalvins, circumdatins, tryptanthrin and its analogues phaitanthrins A-E, methylisatoid, and candidine have been very important targets due to their structural architectures and promising bioactivities [6] .

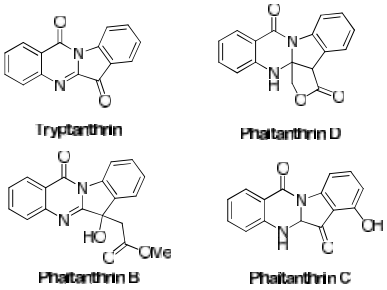


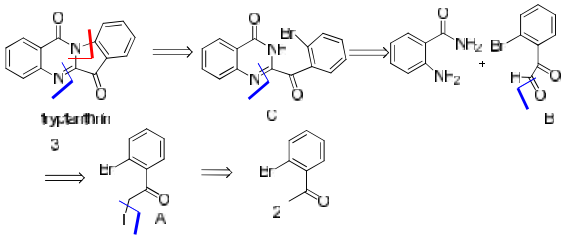
Fig 1: Biologically active quinazoline natural products

In view of the importance of these heterocycles diverse synthetic methods have been developed for synthesis of tryptanthrin. Among these, condensation between isatoic anhydrides and isatins in the presence of triehtylamine or in aqueous β-cyclodextrin solution [9]. Recently, N. P. Argade e*t al.* were synthesized tryptanthrin from Quinazolines esters with aryl TMS triflates in one step reaction [10]. An alternative condensation is the one between ortho-aminobenzoic acid and isatin in the presence of $SOCl_2$ [11-13]. However, many methods still utilized the step-by-step synthetic strategy. Therefore, the development of a efficient and practical, one-pot protocol to access tryptanthrin is both attractive and valuable; it could also have importance in directing further research for one-pot synthesis of other natural products.

In this communication we have reported the synthesis of tryptanthrin (indolo[2,1-*b*]quinazoline-6,12-dione) derivatives with DMSO/I_2 and CuI/K_2CO_3 as catalytic system from Anthranilamideand 2-bromo acetophenone.

2. MATERIALS AND METHODS

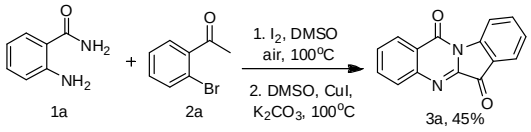
Retrosynthetically (Scheme 1), it was envisioned that tryptanthrin could be achieved from 1&2 assembling four reactions in one pot.while aldehyde B might be furnished from the α-bromo ketone 2 through Kornblum oxidation. It was also thought that **B** could easily cyclised to **C** and **3** furnished *via* intramolecular hetero aryl coupling of **C**.



Scheme 1. Retrosynthetic Analysis

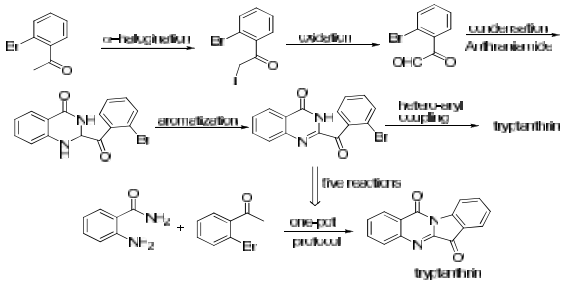
With this consideration, we initially performed reaction with anthranilamide and 2-bromo acetophenone in presence of 30 mol% iodine/DMSO. After 6 hrs. the crude product was reacted with CuI/K_2CO_3 in DMSO at 100°C for 2 hrs. Fortunately, the desired tryptanthrin (**3a**) was obtained in 45% isolated yield (Scheme 2). The product was purified by flash column chromatography on silica gel and characterized by spectroscopic analysis. The spectral data obviously confirm the proposed structure for **3a**.

Scheme 2. An oxidative cyclization/ Hetero aryl coupling reactions leading tryptanthrin.



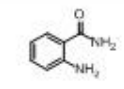
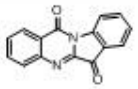
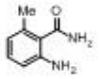
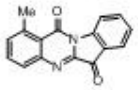
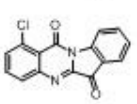
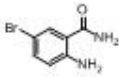
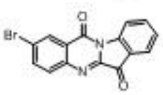
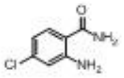
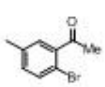
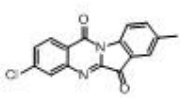
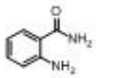
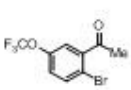
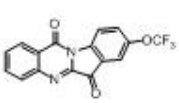
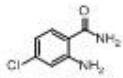
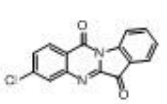
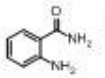
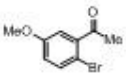
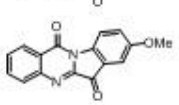
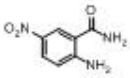
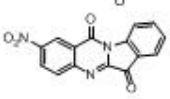
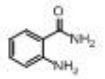
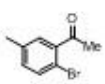
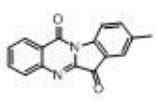
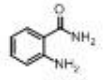
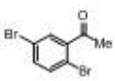
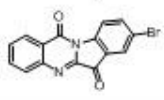
Encouraged by the initial results, the next attempt was made to develop a one-step protocol for the synthesis of tryptanthrin. The synthetic route is described in Scheme 3. It is thought to consist of a α-iodination, Kornblum oxidation, intermolecular condensation, aromatization and hetero arylation reaction sequence. Based on the scheme 3, we wanted to check whether it would be workable to extend a one-pot protocol for the synthesis of tryptanthrin from anthranilamide and 2-bromo acetophenone, wherein five reactions would self-sequentially take place in one-pot (Scheme 3).

Scheme 3. Protocols for Synthesis of tryptanthrin



With this idea in mind, we performed reaction by 2-bromo acetophenone with anthranilamide in one pot reaction. Interestingly, the corresponding product (3a) was obtained in 48% yield. Next we performed reactions for improve the yield of the product, various catalysts, oxidants were investigated in further detail in DMSO. Our delight, the reaction could not perform without I_2/CuI. Therefore, the next reaction was performed with 1.5 equiv of I_2. In fact, improvement in the yield from 45% to 70% was observed by increasing the amount of I_2 from 30 mol% to 1.5 equiv.

Table 1: Scope of the reaction of anthranilamide with 2-bromo acetophenones

Entry	Anthranilamides(1)	2-bromo acetophenone (2)	Product (3)[a]	Yield (%)[b]
a				70
b				61
c				63
d				65
e				63
f				56
g				60
h				61
i				58
j				61
k				59

3. RESULTS & DISCUSSION

Further optimization by screening the reaction temperature showed that a temperature of 100 °C using DMSO as the solvent was optimal for the domino reaction. Lower yield was obtained when the reaction was conducted under an argon or N_2 atmosphere. After several experimental optimizations, we found best optimization conditions were I_2 (1.5 equiv), CuI (0.3 equiv) and K_2CO_3 (1 equiv) in DMSO at 100 ^oC for 6h. Further more the invitro and invivo study to be conducted.

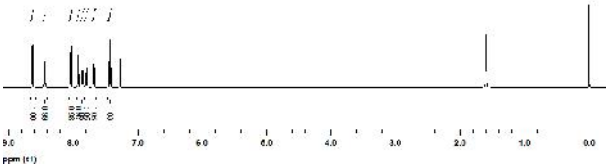


Fig 1: ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound 3a

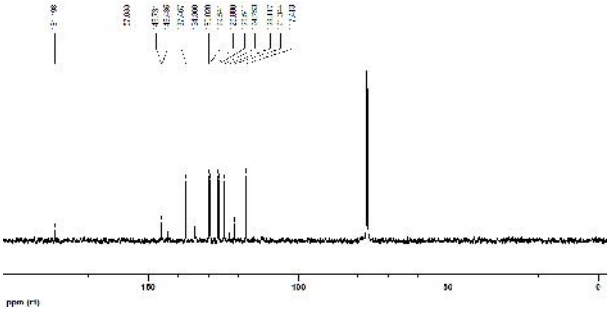


Fig 2: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound 3a

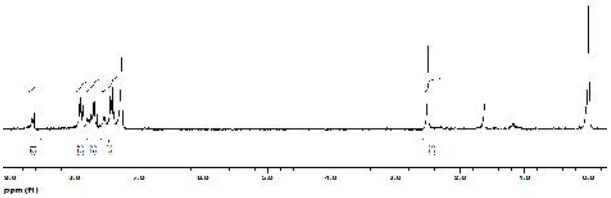


Fig 3: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound 3b

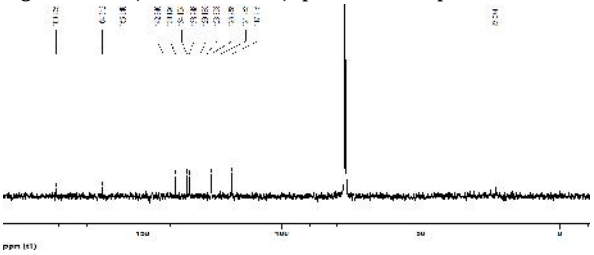


Fig 4: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound 3b

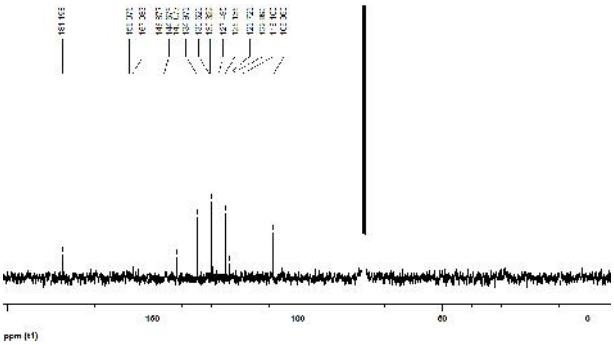


Fig 5: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound 3c

4. ACKNOWLEDGEMENT

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