Synthesis and Biological Evaluation of Some Novel Thiophenes

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Abstract: *A series of tetrahydrobenzothiophene was synthesized with an objective to develop novel and potent antimicrobial agent of synthetic origin. First, N-propylamine and Ethyl cyanoacetate were reacted to yield Propyl cyanoacetamide I. Then, compound (I) was reacted with cyclohexanone to obtain an intermediate, which was processed to 2-amino-3-N-(propylcarboxamido)- 4, 5, 6, 7- tetra hydrobenzo (b) thiophene (II) by well known and versatile Gewald reaction. Reaction of compound II with different aromatic aldehyde yielded the title compound II a-k. The synthesized compound were purified, characterized and evaluated for antimicrobial activity. Most of the compound exhibited moderate to significant activities.*

Keywords: **Tetrahydrobenzothiophene, Schiff bases, Gewald Reaction, Antimicrobial activity.**

1. Introduction

Thiophenes have exhibited an array of biological activities ranging from antibacterial [2, 4, 6, 8, 10, 11], antifungal [2, 9, 25], antioxidant [5], anti-inflammatory activity [1, 5, 10], antihyperlipidemic [6] and so on. Among the antimicrobial agents thiophene derivatives like Cephalothin, Cephalorodine and Cefoxitin are known to have a promising activity. Antifungal agents like Ticonazole and Sertaconazole also contain the thiopheneheterocycle.

So far various new thiophenes have been synthesized and screened in our laboratories for antimicrobial activity. The enthusiastic results prompted us to continue the investigation. So, an attempt was made to synthesize some new substituted thiophenes as antimicrobial agent adapting Gewald reaction [6, 11, 14, 17, 23]. Hence the synthesis of "2-amino-3-N(propylcarboxamido) 4,5,6,7-tetra hydro benzo(b)thiophene" (**I**) is achieved. The different derivatives of the parent compound **I** was achieved by using different aryl aldehydes to obtain a series of Schiff Bases (**II).**

The new compound was characterized by spectral data and screened for their in-vitro antimicrobial (antibacterial and antifungal) activity by agar diffusion method.

2. Materials And Methods

All the reagent were purchased commercially & are used without further purification.

a) Synthesis of Propyl cyanoacetamide I :

A mixture of N-propylamine (0.5M) and ethyl cyano acetate (0.5M) was heated in microwave oven at 750 watt for 2-3min. The reaction mixture was left at room temperature for overnight. The solid obtained was filtered, washed with water and dried. Recrystallization was done by ethanol: water mixture (5 : 1).

b) Synthesis of 2-cyano-2-cyclohexylidene-N-propyl acetamide:

A mixture of propylcyanoacetamide (0.04M), cyclohexanone (0.04 M), ammonium acetate (1g) and glacial acetic acid (2ml) in benzene (80ml) was refluxed with an arrangement for continuous separation of water involving dean stark apparatus. After 10 hours the reaction mixture was cooled, diluted with 10 ml benzene and washed with sodium carbonate solution (10% w/v in water) and water successively and dried over anhydrous sodium sulphate.

The solvent was removed under vacuum and the intermediate crude product obtained was immediately processed for next step.

c) Synthesis of 2-amino-3-N-(propylcarboxamido) 4,5,6,7- tetra hydro benzo (b)thiophene II:

To a mixture of 2-cyano-2-cyano-2-cyclohexylidene-N- propyl acetamide in alcohol (30 ml) was added sulphur (1.28 g; 0.04 M) in portions followed by the addition of, diethyl amine (6.0 ml) drop wise with stirring. The reaction mixture was stirred for 3 hours at 40-45 °C and chilled over night. The solid obtained was filtered, washed with ethanol and crystallized from iso propyl alcohol: water mixture (9 : 1)

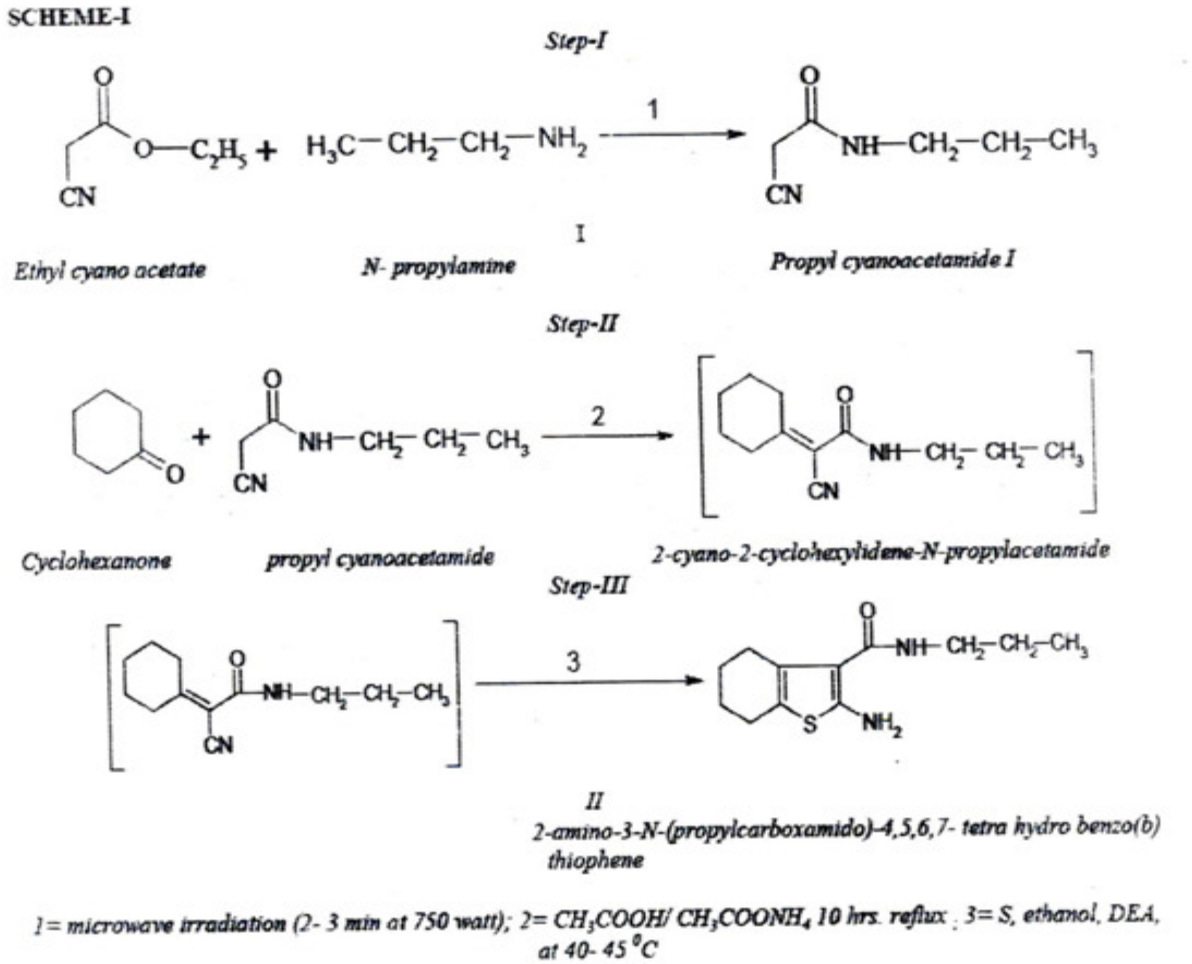
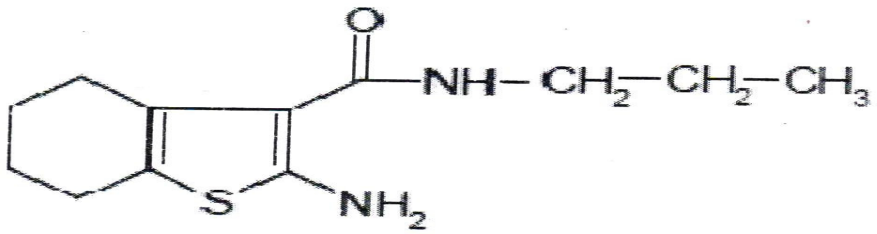


TABLE – 1

2-Amino-3-N-(propyl carboxamido) -4, 5, 6, 7-tetra hydro benzo (b) thiophene (II)

Compound Code	Rx in nm	IR(KBr)cm	^{1}HNMR
II	338	3396,1591(NH_2),3100(Ar CH), 2928(Ali-CH), 1625(C=O); 780(C-S); 1366(Ar-C=C),	8.0 (s, 1H, N-H 4), 6.0(s, 2H, NH_3, 9), 3.3(q, 2H, -$CH_2$3), 26(d, 4H, 2-CH_2, 5 & 8), 1.8(q, 2H, 2), 1.5(m, 4H, 2-$CH_2$6&7), 1.0(t, 3H, -CH_3, 1)



(II)

3.1 Antibacerial Activity:

The antibacterial activity of newly synthesized compound has been evaluated against both gram-positive organisms Staphylococcus aureus and Bacillus subtilies and gram-negative organisms Escherichia coli and Klebsiella pneumonia. The standard drug used was Ampicillin.

The antifungal screening was done by using Aspergillusniger and Candida albicans. The standard drug used was Miconazole nitrate.

The antifungal screening results also suggest that the test compound showed mild to moderate activity against A. niger only but no significant activity against C.albicans compared to the standard employed.

4. Conclusion

Gewald reaction is successfully utilized to synthesize the new 2-amino-3-N-(propyl carboxamido)-4,5, 6, 7-tetrahydro benzo(b) thiophene (II) from the corresponding (I) i.e. propyl cyanoacetamide (SCHEME-I).

A new series of compounds were synthesized from of 2-amino-3-N-(propyl carboxamido)-4,5,6,7tetrahydrobenzo (b) thiophene (II) by microwave irrahydro method,

The formation and purity of the compound was studied by melting point and TLC and are characterized by IR spectrum data of the compound, ^{1}H NMR, data of compound (II) and Mass spectrum data of compound II were analyzed.

The compound was screened for antimicrobial (antibacterial, antifungal) activity. Antibacterial activity agains two Gram positive organisms Staphylococcus aureus and Bacillus subtilis and two Gram negative organisms Escherichia coli and Klebsiella pneumonia using Ampicillin as the standard. The compounds were also screened for their antifungal activity against two strains of fungi Aspergillusniger and Candida albicans using Miconazole nitrate as the standard. All the compounds as well as the standard were used at the concentration of 50 □g/0.1ml.

Evaluation of antibacterial and antifungal activities of all the titled compounds was performed by agar diffusion method. Many of the synthesized compounds showed mild to moderate antimicrobial activity and some were equipotent to the standards employed.

In conclusion, from the antibacterial activity results, it was observed that both electron donating and electron withdrawing groups on the aldehydic phenyl ring of the compounds influenced the activity. But aldehyddic phenyl ring containing electron withdrawing group has shown promising result. Among all the compounds tested, IIf with 2-chloro substitution and IId with 2-nitro substitution at R was found to be most active against both Gram-positive and Gram-negative bacteria. The remaining compounds of both the series exhibited mild to moderate activities when compared to the standards. The antifungal screening results also suggest that the test compounds showed mild to moderate activity against A. niger only but no significant activity against C. albicans compared to the standard employed.

References:

1. *S Srivastava, B Das, 2009. Inter. Jour of Pharma.Scien., 1779-1783.*
2. *S Srivastava, B Das, 2007, Asian J Chem, 19(5), 2813-17.*
3. *Das B, S Srivastava, 2007, Asian J Chem,19(5), 4118-20.*
4. *J Saravanan, 2003, Asian J Chem, 15, 67-70.*
5. *D Singh, 2007, ActaPharmaceuticaSciencia, 49, 29-38.*
6. *VH Bhaskar, 2007, Asian J Chem, 19(7),5187-94.*
7. *Queiroz MJRP et al., 2006, Bioorg Med Chem Letter., 10, 4825-28.*
8. *Tehranchian S et al., 2005, Bioorg Med ChemLettr., 15, 1023-25.*
9. *Kumar Naresh et al. Actaciencia India, Vol:xxxiic, No.3, 307(2008)*
10. *Kumar Naresh et al. J. Chemtrack Vol:16 (2), 505-508, 2014*
11. *Kumar Naresh et al. J. Chemtrack Vol:19 (2), 231-236, 2017*