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Advances in Bioresearch

## ORIGINAL ARTICLE

# Synthesis of 1,2-Diphenyl-thieno[3,2-e]-pyrrolo[1,2-a]-pyrimidin-5(4H)-one derivatives as Antitubercular Agents.

**Badgujar V.L*[1]., Shirole N.L[1]., R.B Patil[1], Wagh R.D[1]**
Department of Pharmaceutical Chemistry, DCS's A.R.A. College of Pharmacy, Nagaon, Dhule(MS), India
*[1]**Corresponding Author** 's Email: vilaspharma007@gmail.com

**ABSTRACT**
*A New series of 1,2-Diphenyl-thieno[3,2-e]-pyrrolo[1,2-a]- pyrimidin-5(4H)-one derivatives were synthesized and the structures of these compounds were established on the basis of spectral data. The title compounds were evaluated for antitubercular activity by L.J. media method. Most of these compounds have shown promising antitubercular activity when compared with the standard drug streptomycin.*
***Keywords:*** *Pyrrolopyrimidine, Antitubercular activity*

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## INTRODUCTION

Tuberculosis (TB) is a contagious and airborne disease caused by *Mycobacterium tuberculosis* bacteria. It is a disease of poverty and mostly TB deaths are in the developing world including the majority of adults in their productive years. Tuberculosis is often seen in those people who have weak immune system and it is the major reason of fatality among those infected with HIV [1,2]. The occurrence of both multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), the indigence for more effective chemotherapy for the treatment of TB [3]. The recent chemotherapy DOTS (directly observed therapy short-course) for TB and DOTS-Plus (DOTS plus Second-line TB drugs) for MDR-TB given compliance treatment has up to 95% cure rate [4], [5]. The fatality of the disease owing to the origin of multidrug-resistant TB poses a challenge to build a novel agent to cure the drug resistant type of TB disease [6]. After many attempts in the design and synthesis of new therapeutic agent by pharmaceutical companies and academic institutions, the recent therapeutic agents are inadequate to cure TB [7]. The currently recommended treatment for latent TB infection is isoniazid given for six to nine months. The long duration of this therapy and the potential toxicities of isoniazid means there is a major compliance problem associated with the treatment regimen. Although new drugs are needed to shorten the duration of treatment of latent TB infection, the safety profile for these drugs must be excellent, because most patients with latent infection are destined never to experience activation of their TB [8]. Therefore, the need for newer, more effective drugs that can achieve multiple goals in improving TB control is pressing. Recognizing these serious facts, we initiated a programme to synthesize and screen diverse heterocyclic entities like pyrrole pyrimidine as potential anti-tubercular agents. Based on our previous results [9], [10],[11] we set upon a programme of making antitubercular agents, using the central thieno[3,2e]pyrrolo[1,2-e]-pyrimidine as the template and adding versatile substituents on the various positions of thiophenpyrimidine ring and subjected them to antimycobacterial screening.

## MATERIAL AND METHODS

All the chemicals used in the synthesis were of laboratory grade. Melting points were determined on an electrothermal apparatus in an open capillary tube and are uncorrected. The ultraviolet absorption spectra were determined in methanol by using a Schimadzu 1600 UV-Visible double beam

Spectrophotometer. The IR spectra of synthesized compounds were recorded on Bruker FT-IR.The 1H NMR spectra were measured on a BRUKER AVANVEI 400 spectrophotometer (Germany) using DMSO-d 6 or $CDCl_3$ as the solvent and chemical shifts were expressed as δvalues in ppm against TMS as an internal standard. TLC using silica gel G 60 3 (Merck, Germany) routinely checked the purity of the compounds and the spots were exposed in iodine vapors for visualization.

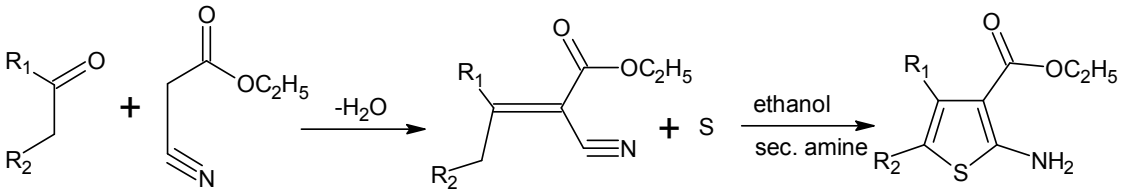
**Synthesis of 2-amino-3-carbethoxythiophenes*(Ia-d)***[12-15].

All the ortho amino esters used in the scheme were prepared by the variants of the well-known Gewald synthesis[12-15]**.**Two different variants have been used to prepare four different thiophene-*o*-aminoesters***(Ia-d)***.

**Method [14]**

This method A is a two-step process. First step is the prior condensation of an aldehyde or ketone (1) with an appropriate cyanomethylene compound (**2**), usually under the influence of sodium or ammonium acetate to obtain α, β-unsaturated nitrile(**3**) (Knoevenagel condensation product which is otherwise known as alkylidine intermediate) in a suitable solvent like benzene. In this step water molecules formed during the reactions were removed using Dean-Stark condenser.

In the second step the alkylidine intermediate is reacted with sulphur in ethanol containing a secondary base such as diethyl amine at around $50^0$C to complete the preparation.

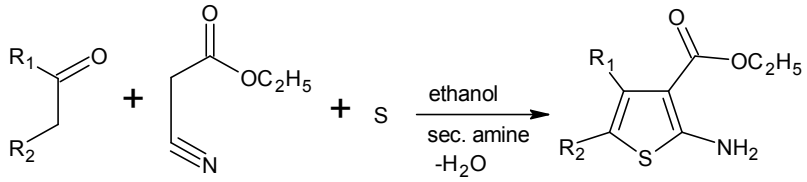



**(1)** **(2)** **(3)** ***(Ia-d)***

In many cases this procedure gives higher yield than method B.

**Method B[14,13]**

It is one pot condensation reaction involving an aldehyde or ketone **(1)** with an active methylene group containing nitrile, (**2**) such as cyanoacetic ester, malononitrile with sulphur in ethanol, in presence of a secondary amine as catalyst at ambient temperature. (Secondary amine used should be 0.5-1.0 mole equivalent of the amount of nitrile used). Here the cyanomethylene compound used is ethyl cyanoacetate.




**(3)** **(2)** ***(Ia-d)***

**Synthesis of 2-Acetamido-3-Carbethoxy Thiophene: (*II*a-*II*f) [16]**

The compound *I*a-*I*f was heated under reflux for 2 hours in the presence of acetic acid/ acetic anhydride (30ml)(1:1).The reaction mixture was cooled and poured into ice-cold water. The precipitated solid was filtered off to obtain the crude product of the acetylated compound(*II*a-*II*f).

**Synthesis of 2-acetamido-3-carbethoxy-5,6-dimethyl thiophene:(*II*a)[16]**

The compound 2-Amino-3-carbethoxy-5,6-dimethyl-thiophene was heated under reflux for 2 hours in the presence of acetic acid/acetic anhydride(30ml)(1:1). The reaction mixture was cooled and poured into ice-cold water. The precipitated solid was filtered off to obtain the crude product acetylated compound(*II*a).

**Synthesis of acetamido-3-carbethoxy-5,6dihydro (4H) cyclopenta [b] thiophene:(*II*b)[16]**

The compound 2-amino-3-carbethoxy-5,6-dihydro-4H-cyclopenta[b]thiophene was heated under reflux for 2 hours in the presence of acetic acid/acetic anhydride(30ml)(1:1). The reaction mixture was cooled and poured into ice-cold water. The precipitated solid was filtered off to obtain the crude product acetylated compound(*II*b).

**Synthesis of 2-acetamido-3-carbethoxy-5-phenylthiophene:(*II*c)[16]**

The compound 2-amino-3-carbethoxy-5-phenylthiophene was heated under reflux for 2 hours in the presence of acetic acid/acetic anhydride(30ml)(1:1). The reaction mixture was cooled and poured into ice-cold water. The precipitated solid was filtered off to obtain the crude product acetylated compound (*II*c).

**Synthesis of 2-acetamido-3-carbethoxy-6-methyl-5-phenylthiophene:(*II*d)[16]**

The compound 2-amino-3-carbethoxy-6-methyl-5-phenyl-thiophene was heated under reflux for 2 hours in the presence of acetic acid/acetic anhydride(30ml)(1:1). The reaction mixture was cooled and poured into ice-cold water. The precipitated solid was filtered off to obtain the crude product acetylated compound(*II*d).

**Synthesis of 2-acetamido-3-carbethoxy-5-(4-chloro)-phenylthiophene:(*II*e)[16]**

The compound 2-amino-3-carbethoxy-5-(4-chloro)phenylthiophene was heated under reflux for 2 hours in the presence of acetic acid/acetic anhydride(30ml)(1:1). The reaction mixture was cooled and poured into ice-cold water. The precipitated solid was filtered off to obtain the crude product acetylated compound(*II*e).

**Synthesis of 2-acetamido-3-carbethoxy-5-(4-bromo)phenylthiophene:(*II*f)[16]**

The compound 2-amino-3carbethoxy-5-(4-bromo)phenylthiophene was heated under reflux for 2 hours in the presence of acetic acid/acetic anhydride(30ml)(1:1). The reaction mixture was cooled and poured into ice-cold water. The precipitated solid was filtered off to obtain the crude product acetylated compound(*II*f).

**Synthesis of 1,2-Diphenyl-4,5-dimethylthieno[3,2-e]- pyrrolo[1,2-*a*]pyrimidin-5(4*H*)-one (*III*a-*III*f)[1,16]**

A mixture of compound (*I I* a - *I I* f ) (10mmol) and benzoin (10mmol) in ethanol was heated under reflux for 1h.The resultant reaction mixture was allowed to concentrated and then cooled at room temperature.This results in separation of a solid which is then filtered off using buckner funnel and recrystallized from methanol to give compound(IIIa-IIIf).

**Synthesis of 1,2-diphenyl-5,6-dimethylthieno[3,2e]pyrrolo[1,2-e]-pyrimidine-5(4H)-one:(*III*a)[16]**

A mixture of compound 2-acetamido-3-carbethoxy-5,6-dimethylthiophene (10mmol) and benzoin(10mmol) in ethanol 30ml was heated under reflux for 1h.The resultant reaction mixture was allowed to concentrated and then cooled at room temperature. This results in separation of a solid which is then filtered off using buckner funnel and recrystallized from methanol to give compound(*III*a) in 70.95%.

**Synthesisof 1,2-diphenyl-5,6-dihydro-(4H)-cyclopentano[b]thiophene-[3,2-e] Pyrrolo- [1,2-e]-pyrimidine-5(4H)-one:(*III*b)**

A mixture of compound 2-acetamido-3-carbethoxy-5,6-dihydro-4H-cyclopenta[b]thiophene (10mmol) and benzoin(10mmol) in ethanol 30ml was heated under reflux for 1h.The resultant reaction mixture was allowed to concentrated and then cooled at room temperature. This results in separation of a solid which is then filtered off using buckner funnel and recrystallized from methanol to give compound(*III*b) in 65.47%.

**Synthesis of 1,2 diphenyl-5-phenylthieno[3,2-e]-pyrrolo[1,2-e]-pyrimidine-5- (4H)-one: (*III*c)**

A mixture of compound 2-acetamido-3carbethoxy-4-phenyl-thiphene (10mmol) and benzoin(10mmol) in ethanol 30ml was heated under reflux for 1hr. The reaction mixture was heated under reflux for 1h.The resultant reaction mixture was allowed to concentrated and then cooled at room temperature. This results in separation of a solid which is then filtered off using buckner funnel and recrystallized from methanol to give compound(*III*c) in 72.08%.

**Synthesis of 1,2diphenyl-6-methyl-5--phenylthieno [3,2-e]-pyrrolo[1,2-e]-Pyrimidie-5-(4H)-one: (*III*d)**

A mixture of compound 2-acetamido-3-carbethoxy-6-methyl-5-phenyl-thiophene (10mmol) and benzoin (10mmol) in ethanol 30ml was heated under reflux for 1hr. was heated under reflux for 1h.The resultant reaction mixture was allowed to concentrated and then cooled at room temparature. This results in separation of a solid which is then filtered off using buckner funnel and recrystallized from methanol to give compound(*III*d) in 51.76%.

**Synthesis of 1,2diphenyl-5-(4-chloro)phenylthieno[3,2e]-pyrrolo[1,2e]pyrimidine 5-(4H) one: (*III*e)**

A mixture of compound 2-acetamido-3-carbethoxy-5-(4-chloro)phenyl-thiopene (10mmol) and benzoin (10mmol) in ethanol 30ml was heated under reflux for 1hr. was heated under reflux for 1h.The resultant reaction mixture was allowed to concentrated and then cooled at room temparature. This results in separation of a solid which is then filtered off using buckner funnel and recrystallized from methanol to give compound (*III*e) in 56.28%.

**Synthesis of 1,2diphenyl-5(4-bromo)phenylthieno[3,2e]-pyrrolo[1,2e]pyrimidine5-(4H) one: (*III*f)**

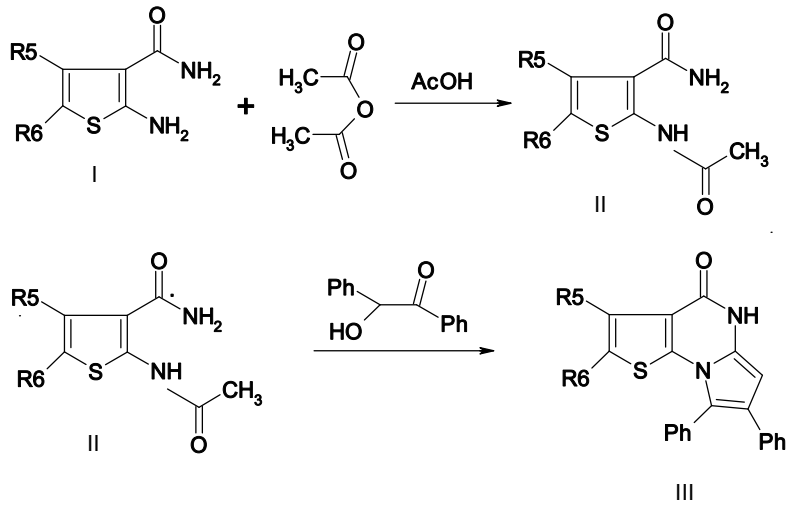
A mixture of compound 2acetamido-3-carbethoxy-5-(4-bromo) phenylthiophene(10mmol) and benzoin (10mmol) in ethanol 30ml was heated under reflux for 1hr. The reaction mixture was heated under reflux

for 1h.The resultant reaction mixture was allowed to concentrated and then cooled at room temperature. This results in separation of a solid which is then filtered off using buckner funnel and recrystallized from methanol to give compound(*III* f) in 77.55%.

**RESULT**

**Synthesis of 1,2Diphenyl-thieno[3,2e]-pyrrolo[1,2-a]pyrimidine-5(4-H)-one(IIIa-IIIf)**

In the present work we have synthesised1,2-Diphenyl-thieno[3,2-e]- pyrrolo[1,2-*a*]pyrimidin-5(4*H*)-one(IIIa-IIIf) with modifications at the substituents attached to the 5 & 6-positions of the thienopyrimidine nucleus. The choice of the substituent pattern was such that a variety of groups having positive and negative contributions to lipophilic, electronic and steric parameters were selected as depicted in **Scheme-I**.




**Scheme I**

**Proposed mechanism is as follows** :

The generation of molecule*III*a-IIIf is proceed via initial acetylation of $NH_2$ group followed by intramolecular cyclization to form pyridine derivative. This step is immediately followed by Intermolecular nucleophilic attack via nitrogen atom of pyridine on the benzoin carbon with removal of water molecule. Finally there is elimination of water molecule through condensation to form the pyrrol derivatives (*III*a-IIIf)

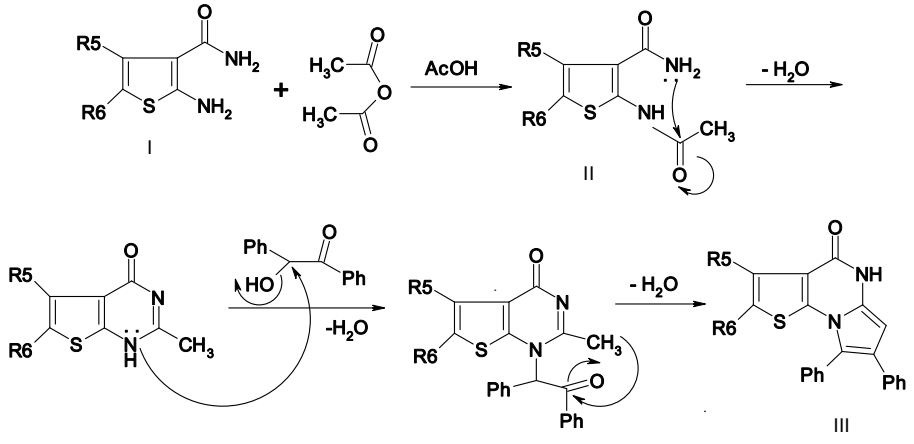
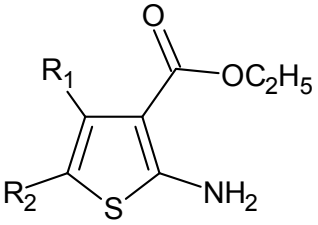


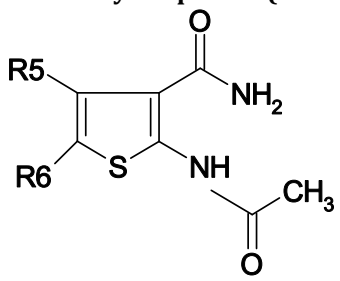
**Table No. 1 Physical and spectral data of compound 2-amino-3-carbethoxy thiophene*(Ia-If)***




| Comp ID | $R_1$ $R_2$ | Mol. Formula | m.p. ºC | Yield (%) | IR in KBr ($cm^{-1}$) |
|---|---|---|---|---|---|
| ***I*a** | $CH_3$ $CH_3$ | $C_9H_{13}NO_2S$ | 92-93 | 76 | 3425, 3312(NH); 3155, 2984, 1657(COOEt). |
| ***I*b** | -$CH_2$-$CH_2$-$CH_2$- | $C_{10}H_{13}NO_2S$ | 82-84 | 67 | 1652 (C=O), 3411, 3296 (NH), 669 (C-S), 2927 (CH) |
| ***I*c** | $C_6H_5$ H | $C_{13}H_{13}NO_2S$ | 92-95 | 65 | 1661 (C=O), 3310, 3336 (N-H), 1102 (C-S), 2950 (CH) |
| ***I*d** | $C_6H_5$ $CH_3$ | $C_{14}H_{15}NO_2S$ | 91-93 | 73 | 3294, 3399(NH); 3154, 3024, 2986,1645($COOE_t$) |
| ***I*e** | 4-CI-$C_6H_4$ H | $C_{13}H_{12}NO_2S$ CI | 101-103 | 70 | 3450, 3333($_{NH}$); 3109, 2890, 1660($_{COOEt}$). |
| ***I*f** | 4-Br-$C_6H_4$ H | $C_{13}H_{12}NO_2S$ Br | 105-108 | 68 | 3447,3329($_{NH}$); 2978, 1658($_{COOEt}$). |

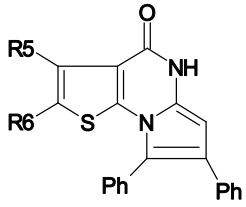
All compounds were recrystallized from methanol and chloroform mixture.

**Table No.2: Physical and spectral data of compound synthesis of 2-Acetamido-3-Carbethoxythiophene: (*II*a-*II*f)**




| Comp ID | $R_5$ $R_6$ | Mol. formula | M.P. ºC | Yield (%) | IR in KBr ($cm^{-1}$) |
|---|---|---|---|---|---|
| ***II*a** | $CH_3$ $CH_3$ | $C_9H_{14}N_2O_2S$ | 96-97 | 71.5 | 3407(NH),1677(C=O),694(CS) |
| ***II*b** | -$CH_2$-$CH_2$-$CH_2$- | $C_{10}H_{16}N_2O_2S$ | 89-91 | 62.47 | 3696(NH),1644,1526(C=O),661(CS) |
| ***II*c** | $C_6H_5$ H | $C_{10}H_{14}N_2O_2S$ | 88-90 | 70 | 3294(NH),1649(C=O) |
| ***II*d** | $C_6H_5$ $CH_3$ | $C_{14}H_{16}N_2O_2S$ | 80-83 | 51.4 | 3241(NH),783,736($C_6H_5$),1662(C=O) |
| ***II*e** | 4-CI-$C_6H_4$ H | $C_{13}H_{13}N_2O_2SCl$ | 97-99 | 52.8 | 965(C6H5),1204(C=O), 3277(NH) |
| ***II*f** | 4-Br-$C_6H_4$ H | $C_{13}H_{13}N_2O_2SBr$ | 118-121 | 56.7 | 3297(NH),789,767($C_6H_5$),1555,1663(C=O) |

**Table No-3: Physical and spectral data of compound of 1,2-Diphenyl-thieno[3,2-e]- pyrrolo[1,2-*a*]pyrimidin-5(4*H*)-one(*III*a-IIIf)**



| Comp ID | $R_5$ $R_6$ | Mol. Formula | M.P.°C | Yield (%) | IR in KBr ($cm^{-1}$) | $^1H$ NMR (δ, ppm) (DMSO-d /CDCl3) |
|---|---|---|---|---|---|---|
| **IIIa** | $CH_3$ $CH_3$ | $C_{23}H_{21}N_2OS$ | 125-128 | 70.95 | 831,754,703($C_6H_5$),1677(C=O),3408,3586(NH) | 1.2989-1.3344(t,2H,$CH_2$), 2.5040-2.5123(t,3H,CH3),3.4354 (s,1H, Pyrrole), 10.9442(s,1H,NH),7.3022-7.5801(m,Ar-H) |
| ***IIIb*** | -$CH_2$- $CH_2$-$CH_2$- | $C_{24}H_{23}N_2OS$ | 110-112 | 65.47 | 3403(NH),830,753($C_6H_5$) | 1.6983-1.7167(t,2H,CH2), 3.8012(s,1H,pyrrole),9.5313(s,1H,NH),7.2197-7.5713(m,Ar-H) 2.2320-2.5079,(t,3H,$CH_3$) |
| ***IIIc*** | $C_6H_5$ H | $C_{27}H_{21}N_2OS$ | 137-140 | 72.08 | 1652(C=O),807($C_6H_5$) | 0.7521-0.7876(t,2H, $CH_2$),2.5034-2.5123(t,3H,$CH_3$),3.5311,(s,1H,pyrrole),11.0005(s,1H,NH), 7.3585-7.4505(m,Ar-H) |
| ***IIId*** | $C_6H_5$ $CH_3$ | $C_{28}H_{23}N_2OS$ | 136-138 | 51.76 | 975,752($C_6H_5$),1202(C=O),3377(NH) | 4.0760-4.1114(t,3H,$CH_3$),0.9354-0.9709(t,2H,$CH_2$),3.6203(s,1H,pyrrole),11.0008(s,1H, NH),7.2550-7.5393(m,Ar-H) |
| ***IIIe*** | 4-CI-$C_6H_4$ H | $C_{27}H_{20}N_2OSCl$ | 134-137 | 56.28 | 975,829($C_6H_5$),1676(C=O),3369(NH) | 4.0760-4.1114(t,3H,$CH_3$),0.9354-0.9709(t,2H,$CH_2$),3.6203(s,1H,pyrrole),11.0008(s,1H,NH),7.2550-7.5393(m,Ar-H) |
| ***IIIf*** | 4-Br-$C_6H_4$ H | $C_{27}H_{20}N_2OSBr$ | 137-140 | 58.37 | 975,830($C_6H_5$),1447,1666(C=O),3358(NH) | 4.0760-4.1218(t,3H,$CH_3$),1.2354-1.3709(t,2H,$CH_2$),4.6203(s,1H,pyrrole),10.0008(s,1H,NH),7.3450-7.5383(m,Ar-H) |

**Antitubercular:**

The Synthesized compounds were evaluated for antitubercular activity by L.J Medium method[17]

**Table No.4. Antitubercular activity of Synthesized compounds**

| Compd. | Concentration | |
|---|---|---|
| | **50mcg/ml** | **100mcg/ml** |
| **IIIa** | - | - |
| **IIIb** | - | - |
| **IIIC** | + | - |
| **IIID** | ++ | ++ |
| **IIIE** | **+-** | **-** |
| **IIIf** | - | - |
| **Streptomycin** | **-** | **-** |

++ : Demotes the growth +- : Demotes the growth with less than 20 colonies

- : Demotes no growth

**DISCUSSION**

2-amino-3-carbethoxythiophenes *(Ia-d)* were prepared by the variants of the well-known Gewald synthesis. Two different variants have been used to prepare four different thiophene-*o*-aminoesters *(Ia-d).* These arethe condensation reaction involving an aldehyde or ketone with an active methylene group containing nitrile, such as cyanoacetic ester, malononitrile with sulphur in ethanol, in presence of a secondary amine as catalyst at ambient temperature afford compound *(Ia-d).*All the intermediate *o*-aminocarbonylthiophenes are pale yellow to brown coloured crystalline solids, freely soluble in chloroform, benzene and methanol. They are all insoluble in water. These compounds are low melting solids (m.p., 68-99°C). They exhibit characteristic $\lambda_{max}$ (methanol) around 332 nm.The solid state (KBr) IR spectra of these compounds reveal a characteristic doublet at around 3400-3300$cm^{-1}$ (N-H) and sharp carbonyl stretching vibration for the ester compound at around 1700-1650 $cm^{-1}$ (C=O).Physical and spectral data of compound 2-amino-3-carbethoxy thiophene*(Ia-f)* given in Table No-1

The compound *I*a-*I*f was heated under reflux for 2 hours in the presence of acetic acid/ acetic anhydride (30ml)(1:1).The reaction mixture was cooled and poured into ice-cold water. The precipitated solid was filtered off to obtain the crude product of the acetylated compound(*II*a-*II*f). All the target compounds are colorless to pale yellow crystalline solids. All are high melting solids (m.p. 80-121°C). They are insoluble in water, benzene and sparingly soluble in dimethylformamide. Most of them exhibit

characteristic absorption ($\lambda_{max}$) at around 260-280 nm (methanol).Appearance of IR bands in the region of 1690-1640 (-N-C=O) and 1600-1500 (C=N) $cm^{-1}$. Spectral data of compound 2-Acetamido-3-carbethoxy thiophene given inTable number 2.

Reaction of a mixture of compound (*II*a - *II*f) (10mmol) and benzoin (10mmol) in ethanol was heated under reflux for 1h.The resultant reaction mixture was concentrated and cooled. The separated solid was filtered off and crystallized from methanol to give targeted 1,2-Diphenyl-4,5-dimethylthieno[3,2-e]-pyrrolo[1,2-*a*]pyrimidin-5(4*H*)-one (*III*a-*III*f)compounds. All the target 1,2-Diphenyl-thieno[3,2-e]-Pyrrolo[1,2-a]pyrimidin-5(4H)one(*III*a-IIIf)compounds were colourless to pale yellow crystalline solids. All have melting solids (m.p. 110-140$^{o}$C). They are insoluble in water, benzene sparingly in methanol and soluble in dimethylformamide. Most of them exhibit characteristic absorption ($\lambda_{max}$) at around 280-320 nm (methanol).Appearance of IR bands in the region of 1690-1640 (-N-C=O) and 1600-1500 (C=N) $cm^{-1}$, also in $^{1}$H-NMR spectrum, signal at 9.5-11.05δ ppm due to $N^{3}$ (amide nitrogen) of pyrimidine ring confirms formation of the product *IIIa-IIIf* given in Table -3.

All the synthesized compounds were screened for antitubercular activity. Compound IIIa, IIIb and IIIf have shown excellent antitubercular activity. However compound IIIc and IIIe has shown moderate antitubercular activity, while compound IIId does not shown antitubercular activity when compared with the standard drug streptomycin.

## CONCLUSIONS

We synthesized a series of 1,2-Diphenyl-thieno[3,2-e]- pyrrolo[1,2-*a*]pyrimidin-5(4*H*)-one(*III*a-IIIf) in high yields; the synthesized IIa-IIf compounds were used as a starting material for the synthesis of compound IIIa-IIIe. The advantages of the obtained IIa-IIf compounds are low cost of the starting chemicals and simple experimental procedure of synthesis. Compound IIIa, IIIb and IIIf have shown excellent antitubercular activity. However compound IIIc and IIIe has shown moderate antitubercular activity, while compound IIId does not shown antitubercular activity when compared with the standard drug streptomycin.

## REFERENCES


1. Nayan H.Bhuva,Pratik K.TalparaPankaj M.SingalaVrajlal K.GothaliyaViresh H.Shah,(2017). Synthesis and biological evaluation of pyrimidinyl sulphonamide derivatives as promising class of antitubercular agents, Journal of Saudi Chemical Society,21, 5, 517-527
2. W.H. Organization (2011). TB/HIV Facts 2011–2012 WHO, Geneva, Switzerland
3. Long R., (2000). Drug-resistant tuberculosis Can. Med. Assoc. J., 163,425-428
4. Corbett.L. , WattC.J. , WalkerN. , MaherD. , Williams,B.G., Raviglione, M.C. , Dye C. , (2003).The growing burden of tuberculosis: global trends and interactions with the HIV epidemic Arch. Intern. Med., 163 pp. 1009-1021
5. R. Loddenkemper, D. Sagebiel, A. (2002). Brendel Strategies against multidrug-resistant tuberculosis Eur. Respir. J., 20,66s-77s
6. G. Di Perri, S. Bonora (2004). Which agents should we use for the treatment of multidrug-resistant *Mycobacterium tuberculosis*J. Antimicrob. Chemother.,54,593-602
7. R.C. Goldman, K.V. Plumley, B.E. Laughon (2007). The evolution of extensively drug resistant tuberculosis (XDR-TB): history, status and issues for global control, Infect. Disord. Drug Targets, 7,73-91
8. Shirole N.L, Talele G.S., Fursule R.A., Shirole K.D., Surana S..J., Jain K. S., (2007)."Synthesis characterization and Pharmacological Evaluation of Novel 2- Substituted thieno[2,3-d]Pyrimidine-4(3H)-Ones Asian Journal,of chemistry,19,7,4985-4992.
9. Shirole N.L, Talele G.S., Fursule R.A., Shirole K.D., Surana S..J., Jain K. S. (2006). "Synthesis And Antihistaminic activity of 2- Alkylamino and 2-Dialkyl aminmethylthieno [2,3- d]Pyrimidines";Asian Journal of chemistry; 18,4, 2673-2679.
10. Badgujar V., Pattan S.R. Bhat A.R., (2005). Synthesis of some pyrazoles and thiozolidinones as antimicrobial agents, Ind. J. Het. Chem., 15,97-98
11. Gewald, K.; (1965). *Angew. Chem*, , 73, 114.
12. Gewald, K.; (165). *Chem. Ber.*, 98, 3571.
13. Gewald, K.; Schinke, E.; Bottcher, H.;(1966). *Chem.Ber.*, 99,94.
14. Tinny, F. J.; Centenko, W.A.; Kerbleski, J.J. (1981). *J. Med. Chem*, 24, 878
15. Ramamurthy S., Jayachandran E., (2015). Synthesis and Characterization of some new 2-Methyl-3-N-Substituted Imino - 5, 6-Tetramethylene Thieno [2, 3-D]-Pyrimidin (3h)–4-ones for Anti-bacterial and Antifungal screening Hygeia.J.D.Med.,7,1,38-45
16. Watt B.R. and Harries G, (1996). Mackie and Mccarthey, Practical medical microbilogy, 331