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Synthesis and Antimicrobial activity of 1,2-Diphenyl-thieno [3,2-e]-pyrrolo [1,2-a]-pyrimidin-5(4H)-one derivatives

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ABSTRACT
Synthesis of 2-amino-3-carbethoxythiophenes (Ia-d) were prepared by the variants of the well-known Gewald synthesis. The recation of these carbethoxythiphenes with acetic acid/acetic anhydride results in 2-Acetamido-3-Carbethoxy Thiophene: (IIa-IIf). When 2-Acetamido-3-Carbethoxy Thiophene reacts with benzoinin ethanol gives targeted 1,2-Diphenyl-4,5-dimethylthieno[3,2-e]- pyrrolo[1,2-a]pyrimidin-5(4H)-one. All the synthesised IIIa-IIIe) compounds were treated evaluated for antifungal activity using Nystatin as a reference standard. The compound IIIe shows strongest antifungal activity than nystatin while compound IIIa, IIIb and IIIc shows moderate antifungal activity.
***Keywords*:** *Pyrrolopyrimidine, Antifungal activity*

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INTRODUCTION

The thieno[2,3-b]pyridine derivatives occupy special place and have attracted considerable attention because of their broad pharmacological activities, including anticancer [1-9], antiviral [10-13], anti-inflammatory [14-17], antimicrobial [18,19], antidiabetic [20-23], antihypertensive [24-26],osteogenic [27,28] and antihistaminic [29,30] activities. The aforementioned biological activities stimulated our interest for the synthesis of several new condensed heterocyclic compounds containing thieno[3,2-e] pyridine moiety condensed with each of pyrrole, hydrazinothienopyrimidine ,cyclopentyl, tetrahydroquinoline, pyrimidine. In view of these reports and as continuation of our earlier studies [29,30],the synthesis of a new series of pyrrolopyrimidine derivatives is now reported. Several compounds were screened for their antimicrobial activity. The new condensed heterocyclic derivatives possessing latent functional substituents appear promising to fulfill the objectives of our biological activity studies and the desired chemical transformations.

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 δ values 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)*.

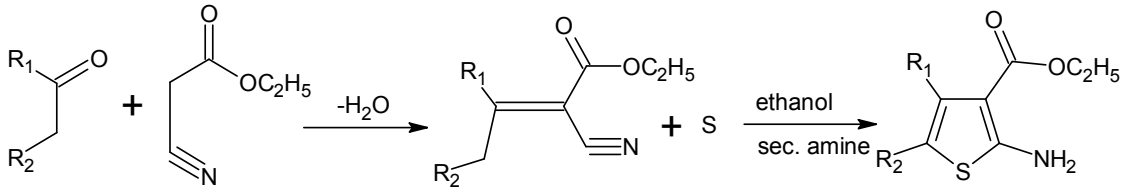
These were prepared by the variants of the well-known Gewald synthesis[31-34] .Two different variants have been used to prepare four different thiophene-*o*-aminoesters***(Ia-d)***.

Method A [33-34]

This method 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 50^0C to complete the preparation.

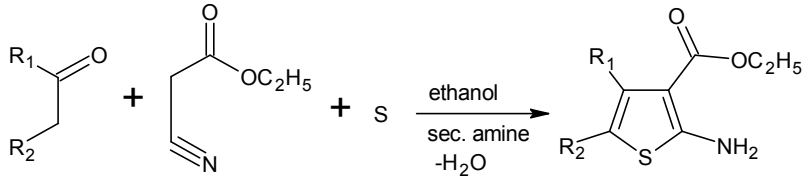


(1) **(2)** **(3)** ***(Ia-d)***

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

Method B [33-34]

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)

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)

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)

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)

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)

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)

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)

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)
A mixture of compound (*II*a - *II*f) (10mmol) and benzoin (10mmol) in ethanol was heated under reflux for 1h.The reaction mixture was concentrated and cooled.The separated solid was filtered off and crystallized from methanol to give compound.

Synthesis of 1,2-diphenyl-5,6-dimethylthieno[3,2e]pyrrolo[1,2-e]-pyrimidine-5(4H)-one: (*III*a)
A mixture of compound 2-acetamido-3-carbethoxy-5,6-dimethylthiophene (10mmol) and benzoin (10mmol) in ethanol 30ml was heated under reflux for 1hr. The reaction mixture was concentrated and cooled. The separated solid was filtered off and crystallized from methanol it give compound(*III*a) in 70.95%.

Synthesis of 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 1hr. The reaction mixture was concentrated and cooled. The separated solid was filtered off and crystallized from methanol it 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 concentrated and cooled. The separated solid was filtered off and crystallized from methanol it give compound(*III*c) in 72.08%.

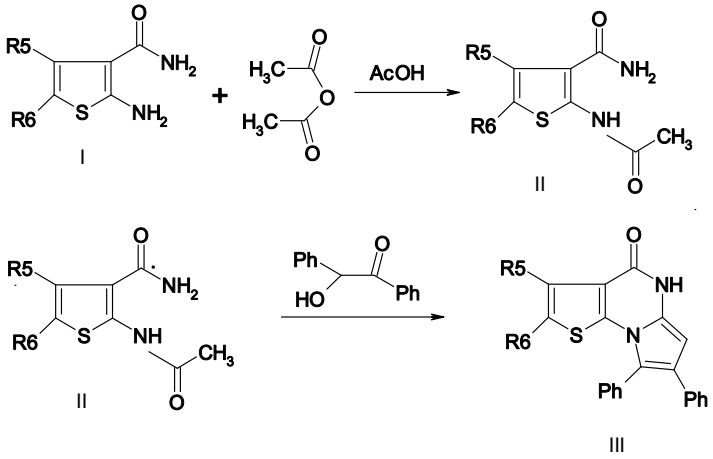
Synthesis of 1,2diphenyl-6-methyl-5--phenylthieno[3,2-e]-pyrrolo[1,2-e]-Pyrimidie-5-(4H)-one: (*III*d)
A mixture of compound 2-acetamido-3-carbethoxy-6-methyl-5-phenyl-thiophene (10mmol) and benzoin (10mmol) in ethanol 30ml was heated under reflux for 1hr. The reaction mixture was concentrated and cooled. The separated solid was filtered off and crystallized from methanol it give compound(*III*d) in 51.76%.

Synthesis of 1,2diphenyl-5-(4-chloro)phenylthieno[3,2e]-pyrrolo[1,2e]pyrimidine5-(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. The reaction mixture was concentrated and cooled. The separated solid was filtered off and crystallized from methanol it give compound (*III*e) in 56.28%.

Synthesis of 1,2diphenyl-5(4-bromo)phenylthieno[3,2e]-pyrrolo[1,2e]pyrimidine 5-(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 concentrated and cooled. The separated solid was filtered off and crystallized from methanol it give compound(*III* f) in 77.55%.

RESULT AND DISCUSSION

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 formation of compound *III*a-f is proceed via initial acetylation of NH_2 group followed by intramolecular cyclization to form pyridine derivative 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)

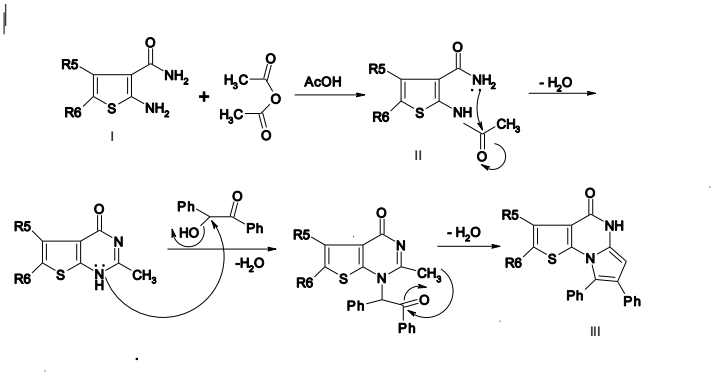
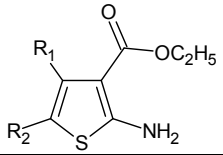


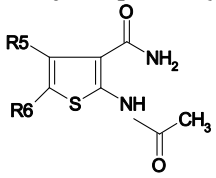
Table No. 1 Physical and spectral data of compound 2-amino-3-carbethoxy thiophene*(Ia-If)*



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($_{COOEt}$).

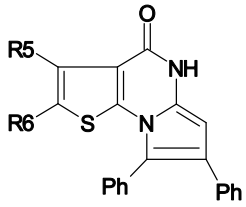
All compounds were recrystallized from methanol and chloroform mixture.

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})
IIa	CH_3 CH_3	$C_9H_{14}N_2O_2S$	96-97	71.5	3407(NH),1677(C=O),694(CS)
IIb	-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)
IIc	C_6H_5 H	$C_{10}H_{14}N_2O_2S$	88-90	70	3294(NH),1649(C=O)
IId	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)
IIe	4-CI-C_6H_4 H	$C_{13}H_{13}N_2O_2SCl$	97-99	52.8	965(C6H5),1204(C=O), 3277(NH)
IIf	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. ºC	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),3408,3 586(NH)	1.2989-1.3344(t,2H,CH_2), 2.5040-2.5123(t,3H,CH3),3.4 354 (s,1H, Pyrrole), 10.9442(s,1H,NH),7.3 022-7.5801(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),7.21 97-7.5713(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_6 H_5)	0.7521-0.7876(t,2H, CH_2),2.5034-2.5123(t,3H,CH_3),3.5 311,(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),120 2(C=O),3377(NH)	4.0760-4.1114(t,3H,CH_3),0.9 354-0.9709(t,2H,CH_2),3.6 203(s,1H,pyrrole),11. 0008(s,1H, NH),7.2550-7.5393(m,Ar-H)
IIIe	4-Cl-C_6H_4 H	$C_{27}H_{20}N_2OSCl$	134-137	56.28	975,829(C_6H_5),167 6(C=O),3369(NH)	4.0760-4.1114(t,3H,CH_3),0.9 354-0.9709(t,2H,CH_2),3.6 203(s,1H,pyrrole),11. 0008(s,1H,NH),7.255 0-7.5393(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),144 7,1666(C=O),3358 (NH)	4.0760-4.1218(t,3H,CH_3),1.2 354-1.3709(t,2H,CH_2),4.6 203(s,1H,pyrrole),10. 0008(s,1H,NH),7.345 0-7.5383(m,Ar-H)

Antimicrobial activity

Some of the synthesized compounds (IIIa-IIIf) were screened for antifungal activity against candida albicans, *Fusarium equiseti* (Corda) Sacc, *Alternaria alternata* (Fr.) Kedissler and *Collectotrichum corchori* Ikata (Yoshida) (Table No.4). The disc diffusion method (19) and poisoned-food techniques (20) was used for antifungal activity.The tested compounds were dissolved in *N,N*-dimethylformamide (DMF) to get a solution of 1 mg mL–1. The inhibition zones were measured in millimeters at the end of an incubation period of 48 h at 28^{0}C. DMF alone showed no inhibition zone. Nutrient agar (NA) and potato dextrose agar

(PDA) were used as basal media to test the fungi. Commercial antifungal nystatin was tested under similar conditions for comparison.

Table No.4. Antifungal activity of some synthesized compounds

Inhibition of mycelial growth (%)[a]				
Compd.	*C. albicans*	*F. equiseti*	*A. alternata*	*C. corchori*
IIIa	58.6	53.8	41.0	27.0
IIIb	62.0	29.0	27.8	14.8
IIIC	70.0	28.0	34.6	36.4
IIID	49.3	40.0	39.5	33.6
IIIE	**95.0**	**70.0**	**52.4**	**48.5**
IIIf	47.5	28.0	32.7	40.0
Nystatin	**71.8**	**44.7**	**51.6**	**40.5**

a 1mgmL–1per disc

RESULTS AND DISCUSSION

2-amino-3-carbethoxythiophenes *(Ia-d)* were prepared by the variants of the well-known Gewald synthesis[1-4] . 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^{o}C). They exhibit characteristic λ_{max} (methanol) around 332 nm.The solid state (KBr) IR spectra of these compounds reveal a characteristic doublet at around 3400-3300cm^{-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^{o}C). They are insoluble in water, benzene and sparingly soluble in dimethylformamide. Most of them exhibit characteristic absorption (λ_{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 (λ_{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 antifungal activity. Compounds IIIe exhibited even stronger activity than nystatin against *C. albicans, F. equiseti, A. alternata and C. corchori.* The compound IIIa, IIIb and IIIc shoes moderate activity against the tested fungi.

CONCLUSION

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. The compound IIIe shows strongest antifungal activity than nystatin while compound IIIa, IIIb and IIIc shows moderate antifungal activity.

REFERENCES

1. Wu JP, Fleck R, Brickwood J, Capolino A and Catron K. (2009), The discovery of thienopyridine analogues as potent IkappaB kinase beta inhibitors. Part II. *Bioorg Med Chem Lett.* 19:5547-51.
2. Willemann C, Grunert R, Bednarski PJ and Troschutz R. (2009). Synthesis and cytotoxic activity of 5,6-heteroaromatically annulated pyridine-2,4-diamines. *Bioorg Med Chem.* 17:4406-19.
3. Lockman JW, Reeder MD, Suzuki K, Ostanin K, Hoff R, Bhoite L, Austin H, Baichwal V and Adam Willardsen J. (2010). Inhibition of eEF2-K by thieno[2,3-b]pyridine analogues. *Bioorg Med Chem Lett.* 20:2283-6.
4. Zeng XX, Zheng RL, Zhou T, He HY, Liu JY, Zheng Y, Tong AP, Xiang ML, Song XR, Yang SY, Yu LT, Wei YQ, Zhao YL and Yang L.(2010). Novel thienopyridine derivatives as specific anti-hepatocellular carcinoma (HCC) agents: synthesis, preliminary structure-activity relationships, and in vitro biological evaluation. *Bioorg Med Chem Lett.* 20:6282-5.
5. Pevet I, Brule C, Tizot A, Gohier A, Cruzalegui F, Boutin JA and Goldstein S. (2011). Synthesis and pharmacological evaluation of thieno[2,3-b]pyridine derivatives as novel c-Src inhibitors. *Bioorg Med Chem.* 19:2517-28.
6. Mohareb RM, Wardakhan WW, Elmegeed GA and Ashour RM. (2012). Heterocyclizations of pregnenolone: novel synthesis of thiosemicarbazone, thiophene, thiazole, thieno[2,3-b]pyridine derivatives and their cytotoxicity evaluations. *Steroids.* 77:1560-9.
7. Feng L, Reynisdóttir I and Reynisson J. (2012). The effect of PLC-g2 inhibitors on the growth of human tumour cells. *Eur. J. Med.Chem.* 54:463-469.
8. Dai XY, Zeng XX, Peng F, Han YY, Lin HJ, Xu YZ, Zhou T, Xie G, Deng Y, Mao YQ, Yu LT, Yang L and Zhao YL. (2012). A novel anticancer agent, SKLB70359, inhibits human hepatic carcinoma cells proliferation via G0/G1 cell cycle arrest and apoptosis induction. *Cell Physiol Biochem.* 29:281-90.
9. Mohareb R.M, Abdallah A.E and Abdelaziz M.A. (2013). New approaches for the synthesis of pyrazole, thiophene, thieno[2,3-b]pyridine and thiazole derivatives together with their anti-tumor evaluations. *Med. Chem. Res*. 109-123.
10. Schnute ME, Anderson DJ, Brideau RJ, Ciske FL and Collier SA.(2007). 2-Aryl-2-hydroxyethylamine substituted 4-oxo-4,7-dihydrothieno[2,3-b]pyridines as broad-spectrum inhibitors of human herpesvirus polymerases. *Bioorg Med Chem Lett.* 17:3349-53.
11. Pinheiro L.C.S, Borges J.C, Oliveira C.D, Ferreira V.F and Romeiro G.A.(2008). Synthesis of new (phenylamino)thieno [2,3-b]pyridines and derivatives of the novel benzo [b] thieno[3,2-h]-1,6-naphthyridinetetracyclic system. *Arkivoc.* 17:77-87.
12. Shuck-Lee D, Chen F.F, Willard R, Raman S and Ptak R.(2008). Heterocyclic Compounds That Inhibit Rev-RRE Function and Human Immunodeficiency Virus Type 1 Replication. *Antimicrob. Agents Chemother.* 52:3169-3179 .
13. Chaubey A and Pandeya S.N. (2011). Pyridine" a versatile nucleuse in pharmaceutical field. *Asian J. Pharm. Clin. Res.* 4:5-8.
14. Boschelli DH, Wu B, Barrios Sosa AC, Chen J, Asselin M, Cole DC, Lee J, Yang X and Chaudhary D. (2008). Synthesis and PKCtheta inhibitory activity of a series of 4-(indol-5-ylamino)thieno[2,3-b]pyridine-5-carbonitriles. *Bioorg Med Chem Lett.* 18:2850-3.
15. Nathan Tumey L, Boschelli DH, Lee J and Chaudhary D. (2008). 2-Alkenylthieno[2,3-b]pyridine-5-carbonitriles: Potent and selective inhibitors of PKCtheta. *Bioorg Med Chem Lett.*, 18:4420-3.
16. Madhusudana K, Shireesha B, Naidu VG, Ramakrishna S, Narsaiah B, Rao AR and Diwan PV. Anti-inflammatory potential of thienopyridines as possible alternative to NSAIDs. *Eur J Pharmacol.* 2012; 678:48-54.
17. Liu H, Li Y, Wang XY, Wang B, He HY, Liu JY, Xiang ML, He J, Wu XH and Yang L.(2013). Synthesis, preliminary structure-activity relationships, and in vitro biological evaluation of 6-aryl-3-amino-thieno[2,3-b]pyridine derivatives as potential anti-inflammatory agents. *Bioorg Med Chem Lett.* 23:2349-52.
18. Bernardino AM, da Silva Pinheiro LC, Rodrigues CR, Loureiro NI, Castro HC, Lanfredi-Rangel A, Sabatini-Lopes J, Borges JC, Carvalho JM, Romeiro GA, Ferreira VF, Frugulhetti IC and Vannier-Santos MA. (2006). Design, synthesis, SAR, and biological evaluation of new 4-(phenylamino)thieno[2,3-b]pyridine derivatives. *Bioorg Med Chem.* 14:5765-70.
19. Al-Trawneh SA, El-Abadelah MM, Zahra JA, Al-Taweel SA, Zani F, Incerti M, Cavazzoni A and Vicini P.(2011). Synthesis and biological evaluation of tetracyclic thienopyridones as antibacterial and antitumor agents. *Bioorg Med Chem.* 19:2541-8.
20. Moretto AF, Kirincich SJ, Xu WX, Smith MJ, Wan ZK, Wilson DP, Follows BC, Binnun E, Joseph-McCarthy D, Foreman K, Erbe DV, Zhang YL, Tam SK, Tam SY and Lee J.(2006). Bicyclic and tricyclic thiophenes as protein tyrosine phosphatase 1B inhibitors. *Bioorg Med Chem.* 14:2162-77.
21. Bahekar RH, Jain MR, Goel A, Patel DN, Prajapati VM, Gupta AA, Jadav PA and Patel PR.(2007). Design, synthesis, and biological evaluation of substituted-N-(thieno[2,3-b]pyridin-3-yl)-guanidines, N-(1H-pyrrolo[2,3-b]pyridin-3-yl)-guanidines, and N-(1H-indol-3-yl)-guanidines. *Bioorg Med Chem.* 15:3248-65.
22. Bahekar RH, Jain MR, Jadav PA, Prajapati VM, Patel DN, Gupta AA, Sharma A, Tom R, Bandyopadhya D, Modi H and Patel PR. (2007). Synthesis and antidiabetic activity of 2,5-disubstituted-3-imidazol-2-yl-pyrrolo[2,3-b]pyridines and thieno[2,3-b]pyridines. *Bioorg Med Chem.* 15:6782-95.
23. Kamata M, Yamashita T, Kina A, Funata M, Mizukami A, Sasaki M, Tani A, Funami M, Amano N and Fukatsu K. (2012). Design, synthesis, and structure-activity relationships of novel spiro-piperidines as acetyl-CoA carboxylase inhibitors. *Bioorg Med Chem Lett.* 22:3643-7.

24. Adachi I, Hiramatsu Y, Ueda M and Kawakami M. (1987). 4,7-dihydrothieno[2,3-b] pyridine derivatives useful in the treatment of cardiovascular diseases. *US Patent.* 4:703-051.
25. Adachi I, Yamamori T, Hiramatsu Y, Sakai K, Mihara S, Kawakami M, Masui M, Uno O and Ueda M.(1988). Studies on dihydropyridines. III. Synthesis of 4,7-dihydrothieno [2,3-b]-pyridines with vasodilator and antihypertensive activities. *Chem Pharm Bull (Tokyo).* 36:4389-402.
26. Ueda M, Matsumura S, Masui M, Matsuura E, Kawakami M, Fujitomo H, Umeda T, Kagawa H, Hirohata S, Shima K and et al. (1993). Pharmacological studies on a new dihydrothienopyridine calcium antagonist. 3rd communication: antihypertensive effects of S-(+)-methyl-4,7-dihydro-3-isobutyl-6-methyl-4-(3-nitrophenyl) thieno[2, 3-b] pyridine-5-carboxylate in hypertensive rats and dogs. *Arzneimittel forschung.* 1993; 43:1282-90.
27. Ohba S, Nakajima K, Komiyama Y, Kugimiya F, Igawa K, Itaka K, Moro T, Nakamura K, Kawaguchi H, Takato T and Chung UI. (2007). A novel osteogenic helioxanthin-derivative acts in a BMP-dependent manner. *Biochem Biophys Res Commun.* 357:854-60
28. Saito K, Nakao A, Shinozuka T, Shimada K, Matsui S, Oizumi K, Yano K, Ohata K, Nakai D, Nagai Y and Naito S. Discovery and structure-activity relationship of thienopyridine derivatives as bone anabolic agents. *Bioorg Med Chem.* 2013; 21:1628-42.
29. 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.
30. 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.
31. Gewald, K.;*Angew. Chem*, (1961)., 73, 114.
32. Gewald, K.; *Chem. Ber.*, (1965), 98, 3571.
33. Gewald, K.; Schinke, E.; Bottcher, H.(1966).;*Chem.Ber*., 99,94.
34. Tinny, F. J.; Centenko, W.A.; Kerbleski, J.J.(1981). *J. Med. Chem*, 24, 878.

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