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SYNTHESIS AND CHARACTERIZATION OF SOME NEW 2-METHYL-3-N-SUBSTITUTED IMINO - 5, 6-TETRAMETHYLENE THIENO [2, 3-D]-PYRIMIDIN (3*H*)–4-ONES FOR ANTI-BACTERIAL AND ANTIFUNGAL SCREENING

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ABSTRACT

Plan: *To synthesize some Schiff bases of 2-Methyl-3-N-amino-5, 6-disubtituted thieno [2, 3-d] - pyrimidin (3H)-4-ones for antibacterial and antifungal activities.*

Preface: *Organic compounds containing thiophene and pyrimidine form a significant group of drugs and known for pharmacological activities having various therapeutic applications. The compounds containing Thieno(2,3-b) pyrimidine nucleus posses broad range of pharmacological activities namely antibacterial, antifungal, trichomicidal, anti-malarial, anti-inflammatory activity ,etc.Thus a new series of Thieno[2,3-d]- pyrimidinones have been synthesized by reacting the active 3-amino group with various substituted aryl aldehydes and screened for antibacterial and antifungal activity.*

Methodology*: In our present investigation we have prepared the intermediate* ***S-2*** *starting from cyclohexanone and ethyl cyano acetate, involving the elegant method described by Gewald et.al. This compound* ***S-2*** *was treated with acetic anhydride followed by hydrazine hydrate to yield the parent compound* ***RJ-2****.This compound was derivatized to various Schiff bases by treating with various substituted aryl aldehydes. The synthesized title compounds were characterized by MP, TLC, UV and a few representative compounds by IR, NMR & Mass spectrum. The compounds were screened for antibacterial and antifungal activity.*

Outcome *: The new title compounds possessing 'electron withdrawing groups' on the aldehydic phenyl ring (RJ-2d, RJ-2j, RJ-2f, RJ-2l) exhibited better antibacterial and antifungal activity compared to the compounds possessing 'electron donating groups'(RJ-2e, RJ-2k, RJ-2m)*

1. INTRODUCTION

In recent years, heterocyclics containing nitrogen and sulphur provide considerable pharmacological and synthetic interest owing to their extensive biological activities, and these are extremely versatile building blocks for the manufacture of bioactive compounds in pharmaceutical drug design.

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This helped medicinal chemists to plan, organize and implement new approaches on discovery of novel drugs and their molecular modifications. Thiophenes and pyrimidines are important class of heterocyclics reported to possess wide spectrum of biological activities such as antibacterial, antifungal, anti inflammatory, CNS depressant, analgesic, antitumor activity and so on.[1-9]

Among all the heterocyclic derivatives, the class of multicycle compounds bearing thienopyrimidine nucleus exhibit a diversity of pharmacological effects such as antibacterial, antifungal, kinase inhibition, immunosuppressive, antidiabetic and anticancer activity .Up to now, there are many different structures containing thienopyrimidine nucleus have been synthesized and evaluated for biological activities.[10-17] Similarly, the Shiff bases have also been reported to possess an array of biological activities namely antimicrobial, ulcerogenic, anti HIV, anticonvulsant, and CNS depressant activities[18-21]

The promising bioactive diversity of these class of heterocyclic compounds and Schiff bases urged us to synthesize and biologically evaluate a series of novel structural variants of thieno [2, 3-d] pyrimidinone derivatives. We have synthesized and utilized 3-amino 2-methyl 4, 5-tetramethylene thieno [2, 3-d] pyrimidin (3*H*)-4-one as key prototype structural unit, and treated the 3- active amino group with substituted aryl aldehydes to get a new series of Schiff bases.

2. EXPERIMENTAL.

The parent compound and the title compounds were prepared as per the scheme. Melting points were determined in open capillary tubes and uncorrected. TLC was carried out using silica gel G with solvents as Benzene: Chloroform (1:1) to find the purity of synthesized compounds. The NMR spectra were recorded in $CDCl_3$ using TMS as internal standard. The IR spectra of the compounds were recorded using KBr pellet on FTIR spectrophotometer and frequencies are recorded in wave numbers. MS was recorded on Brucker DPX.

2.1 Scheme of synthesis.

Step 1.Synthesis of 2-Amino-3- carbethoxy-4, 5- tetramethylene thiophene ***(S-2)***

To the mixture of cyclohexanone (3.92g; 0.04 mol), ethyl cyanoacetate (4.52g; 0.04 mol) and sulphur powder (1.28 g; 0.04 mol) in ethanol (40 ml), diethylamine (4.0 ml) was added drop wise with stirring. The mixture was stirred further for 1hr at 45-50^{0}C, chilled overnight and the solid obtained was filtered, washed and recrystallized from ethanol. Yield 46.87%, M.P 84^{o}C, Rf value 0.6 [Solvent system- Benzene: Chloroform (1:1)]

*Step 2. Synthesis of 2-Acetamido-3- carbethoxy-4, 5- tetramethylene thiophene (**S 2 a**)*

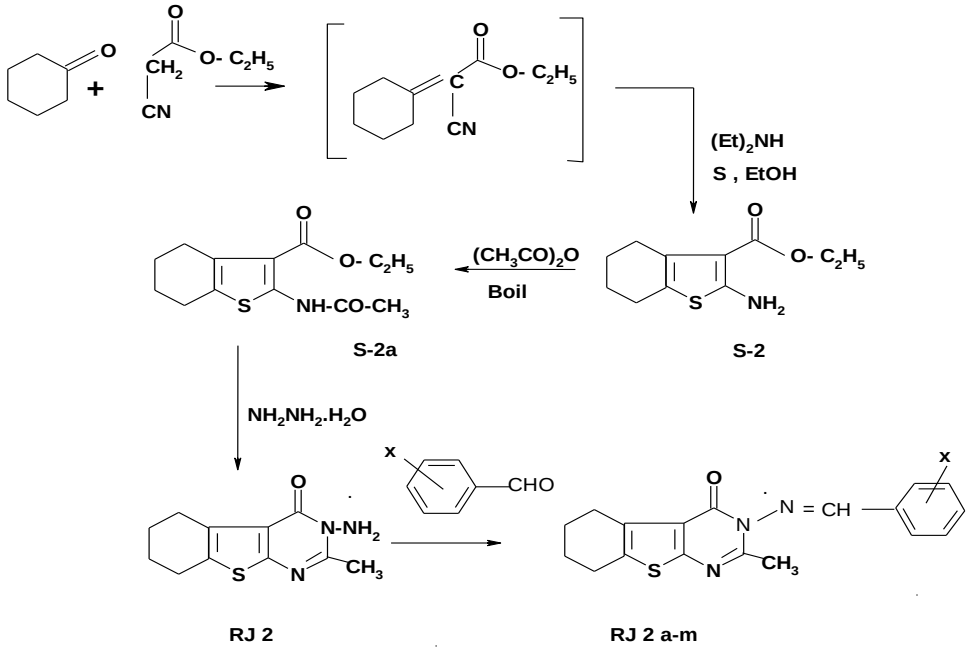
A mixture of S **2** (2.25g; 0.01 mol), acetic anhydride (6.0ml) and zinc dust (0.25g) was stirred and irradiated with microwave heating involving Kenstar microwave oven (2450 MHz, 900 w) for 15 seconds. When the solid dissolved the reaction mixture was cooled and the resulting white solid was crystallized from ethanol-water. Yield 78.25%, M.P 114^{o}C, Rf value 0.53 [Solvent system- Benzene: Chloroform (1:1)]

Step 3. Synthesis of 3-N-amino-2-methyl-5, 6-tetramethylene thieno [2, 3-d]-pyrimidin (3H) – 4-one (**RJ 2)**

A mixture of **S-2 a** (2.67 g, 0.01 mol), hydrazine hydrate (15 ml) and ethanol (20 ml) was irradiated for 20 seconds until the solid is dissolved, the irradiation was continued until solid separates out from the reaction mixture. Then the reaction mixture was cooled to room temperature, a white crystalline product was obtained which was crystallized from aqueous acetone (1:2). Yield 60.42%, M.P 180^{o}C, Rf value 0.59 [Solvent system- Benzene: Chloroform (1:1)]

*Step 4. General method for the Syntheses of 3-N-[(substituted aryl)-methylene imino] -2 methyl, 5, 6-tetramethylene thieno [2, 3-d] - pyrimidin (3H) –4-ones (**RJ-2a-m**)*

A mixture of starting compound **RJ-2** (2.35g; 0.01 mol) and the appropriate aryl aldehydes (0.01 mol) in isopropanol containing catalytic amount of glacial acetic acid (2 ml) was irradiated for 20 seconds then the mixture was cooled to get the corresponding title compounds **(RJ-2a-m)** and are crystallized from propanol or ethyl acetate to obtain the pure compounds.



Code	*X*	*Code*	*X*
RJ-2a	4'-N $(CH_3)_2$	RJ-2h	4'-OH
RJ-2b	4'-CH_3	RJ-2i	-H
RJ-2c	3',4'- $(OCH_3)_2$	RJ-2j	4'-Cl
RJ-2d	2'-Cl	RJ-2k	4'-OH,3'-OCH_3
RJ-2e	4'-OCH_3	RJ-2l	3'-NO_2
RJ-2f	2'-NO_2	RJ-2m	3',4',5'--$(OCH_3)_3$ $(OCH_3)_3$
RJ-2g	2'-OH		

2.2 Antibacterial activity.

The antibacterial activity of the synthesized compounds was determined by agar diffusion method[22] against Gram + ve (*S.aureus, B.subtilis)* and Gram – ve (*E.coli, KPN)* bacteria. Ampicillin was taken as standard reference drug. Stock solutions of newly synthesized compounds and the standard were prepared in DMSO to get a concentration of 50 mcg/0.1ml. The responses of organisms to the synthesized compounds were measured as mean of three values and compared with the response of the standard. Standard deviation was also calculated. (Table-2)

2.3. Antifungal activity.

The antifungal activity was carried out by agar diffusion method[23] against the fungi AN, CA, and CNE. Miconazole nitrate was taken as standard reference drug. Stock solutions of newly synthesized compounds and the standard were prepared in DMSO to get a concentration of 50 mcg/0.1ml. The responses of organisms to the synthesized compounds were measured as mean of three values and compared with the response of the standard. Standard deviation was also calculated. (Table-3)

2.4. Spectral data.

IR (KBr) cm^{-1} Compound **RJ-2**: 3430**.**33(-NH), 3158.65(Ar-CH), 2940.96(S-CH), 1681.12(C=O, aryl), 1530.34 (-N– C = O cyclic stretching), 1634.12(NH bend), 821.90(C-N), 754.35(C-S)

Compound **RJ-2e**: 3382.41(-NH), 3065.13(Ar-CH), 2945.54(S-CH), 1686.44(C=O, aryl), 1660.14(NH bend), 1471(Ar-C=C-), 1522.12 (-N– C = O cyclic stretching), 878.51(C-N), 758.51(C-S)

UV- λ max
Compound **S-2**: 234 nm, Compound **RJ-2**: 214 nm. , Compound **RJ-2e**:212 nm

^{1}NMR ($CDCl_3$)

Compound **RJ 2** : 1.9 (m,4H,-CH_2-dimethylenic protons of cyclohexane ring) ,2.5 (s ,3H ,-CH_3), 2.7 & 2.9 (t,4 H- CH_2- dimethylenic protons of cyclohexane ring), 3.3 (s, solvent peak of DMSO), 5.8 (s, 2 H, -NH_2).

Compound **RJ 2b**: 1.8 (m, 4H,-CH_2-dimethylenic protons of cyclohexane ring), 2.4 & 2.5 (s ,6H ,-CH_3), 2.7 & 3.0 (t,4 H-CH_2-dimethylenic protons of cyclohexane ring), 7.2 & 7.8 (d, 4H of aromatic protons), 8.8 (s, 1H, -N=CH-)

Compound **RJ 2j**: 1.8 (m, 4H,-CH_2-dimethylenic protons of cyclohexane ring), 2.5 (s, 3H,-CH_3), 2.7 & 3.0 (t, 4 H- CH_2-dimethylenic protons of cyclohexane ring), 7.4 & 7.8 (d, 4H of aromatic protons), 8.9 (s, 1H, -N=CH-)

Compound **RJ 2 m**: 1.8 (m, 4H,-CH_2-dimethylenic protons of cyclohexane ring), 2.5 (s, 3H,-CH_3), 2.7 & 2.9 (t, 4 H- CH_2-dimethylenic protons of cyclohexane ring), 3.8 (s, 9H of trimethoxy protons), 7.1 (s, 2H of aromatic protons), 8.8 (s, 1H, - N=CH)

Mass spectral data

RJ-2a: Ms: 366(100%), 242(55%), 193(60%), 169(32%) and 120(30%).
RJ-2g: Ms: 339(100%), 246(50%), 193(58%), 146(38%) and 93(33%).

Table-1 Physical data of the compounds synthesized.

Code	*X*	*Molecular Formula*	*M.W*	*% Yield*	*M.P. (ºC)*	R_f *Value*
RJ 2 a	4'Dimethylamino	$C_{20}H_{22}ON_4S$	366	52.2	188	0.56
RJ 2 b	4'-Methyl	$C_{19}H_{19}ON_3S$	337	54.5	162	0.72
RJ 2 c	3',4'-Dimethoxy	$C_{20}H_{21}O_3N_3S$	383	52.2	200	0.58
RJ 2 d	2'-Chloro	$C_{18}H_{16}ON_3S$	357	63.5	210	0.54
RJ 2 e	4'-Methoxy	$C_{19}H_{19}O_2N_3S$	353	58.4	192	0.47
RJ 2 f	2'-Nitro	$C_{18}H_{16}O_3N_4S$	368	66.4	174	0.88
RJ 2 g	2'-Hydroxy	$C_{18}H_{17}O_2N_3S$	339	67.6	206	0.64
RJ 2 h	4'-Hydroxy	$C_{18}H_{17}O_2N_3S$	339	58.4	212	0.58
RJ 2 i	H	$C_{18}H_{17}ON_3S$	323	63.2	170	0.70
RJ 2 j	4'-Chloro	$C_{18}H_{16}ON_3S$	357	68.5	222	0.68
RJ 2 k	4'-hydroxy-3'methoxy	$C_{19}H_{19}O_3N_3S$	369	64.0	176	0.56
RJ 2 l	3'-Nitro	$C_{18}H_{16}O_3N_4S$	368	66.7	190	0.68
RJ 2 m	3',4',5'-Trimethoxy	$C_{21}H_{23}O_4N_3S$	413	74.4	208	0.65

Table-2 Antibacterial activity of the synthesized compounds.

Code	X	Zone of inhibition (mm) mean ± S.D			
		S.aureus	*B.subtilis*	*E.coli*	*K.pneumoniae*
RJ 2 a	4' Dimethyl amino	13.33±0.57	15.66±1.15	NA	NA
RJ 2 b	4'-Methyl	13.66±0.57	13.66±1.15	NA	NA
RJ 2c	3',4'-Dimethoxy	14.00±1.00	12.00±1.73	14.66±1.52	14.66±1.52
RJ 2 d	2'-Chloro	18.66±0.57	18.33±1.52	17.66±1.88	17.00±1.73
RJ 2 e	4'-Methoxy	15.66±1.15	13.00±1.73	NA	NA
RJ 2 f	2'-Nitro	18.33±1.15	17.33±1.15	19.33±0.57	17.00±0.00
RJ 2 g	2'-Hydroxy	15.66±0.57	14.66±1.15	NA	NA
RJ 2 h	4'-Hyroxy	15.66±1.88	14.00±1.73	NA	NA
RJ 2 i	H	15.00±1.00	15.33±1.15	11.66±0.57	11.33±1.52
RJ 2 j	4'-Chloro	21.33±1.52	18.33±1.15	20.66±0.57	17.66±0.57
RJ 2 k	4'-Hyroxy3'methoxy	12.00±1.00	11.66±1.52	14.66±1.52	13.66±0.57
RJ 2 l	3'-Nitro	18.66±1.52	18.00±1.73	18.33±1.15	18.66±1.41
RJ 2 m	3'4'5'Trimethoxy	12.66±1.15	12.33±1.15	13.33±0.57	12.66±1.15
Ampicillin	.....	22.66±0.57	18.00±1.00	23.33±0.57	18.33±1.15

Table-3 Antifungal activity of the synthesized compounds

Code	X	Zone of inhibition(mm)		
		A.niger	*C.albicans*	*C.neoformans*
RJ 2 a	4’ Dimethyl amino	08.33±0.57	NA	09.00±1.00
RJ 2 b	4’-Methyl	08.66±0.57	NA	06.66±0.57
RJ 2c	3’,4’-Dimethoxy	10.66±1.15	07.66±1.52	10.33±1.15
RJ 2 d	2’-Chloro	14.66±1.52	11.66±1.15	13.66±0.57
RJ 2 e	4’-Methoxy	09.33±1.52	NA	07.66±1.52
RJ 2 f	2’-Nitro	15.66±1.15	14.66±1.52	14.00±1.00
RJ 2 g	2’-Hydroxy	10.33±1.15	09.33±1.52	08.66±0.57
RJ 2 h	4’-Hyroxy	11.66±1.15	08.33±1.52	10.66±1.15
RJ 2 i	H	08.00±1.00	NA	07.33±0.57
RJ 2 j	4’-Chloro	16.33±0.57	15.00±1.00	14.66±1.52
RJ 2 k	4’-Hyroxy 3’-methoxy	10.33±1.52	10.33±1.15	07.66±1.52
RJ 2 l	3’-Nitro	15.66±1.15	14.66±1.52	14.33±1.52
RJ 2 m	3’4’5’-Trimethoxy	09.33±1.52	08.66±0.57	09.00±1.73
Miconazole nitrate	.....	27.33±1.52	25.33±1.15	23.33±1.52

3. RESULTS AND DISCUSSION

The formation of the intermediate **S-2** has been clearly indicated by its IR spectrum showing a characteristic absorption band at 3450 cm^{-1} and 3310 cm^{-1} arising from the asymmetric and symmetric stretching vibrations of the amino group and there is the appearance of a sharp band at 2940 cm^{-1} due to – S – CH – group. The compound **RJ -2** which was obtained by the cyclization of **S-2a** showed no absorption band at 1620 cm^{-1} due to the absence of the CO group of the ester but the compounds **RJ-2** & **RJ-2e** exhibited characteristic strong peak at 1680 cm^{-1} (C = O cyclic) due to the presence of pyrimidine ring (aromatic compound containing carbonyl system). There is one more strong peak due to pyrimidine ring at 1540 cm^{-1} which is due to -N– C = O cyclic stretching vibration. The formation of RJ-2e from RJ-2 is confirmed by the disappearance of –NH- peak at 3282 cm^{-1} and appearance of new peak at 1568 cm^{-1} due to imino group.

The UV absorption spectrum of the compound S-**2** exhibited a λ max at 234 nm and the compound **RJ-2** & **RJ-2e** exhibited λ max at 214 nm respectively. This hypsochromic shifts with reduction in intensity clearly indicates the cyclic hetero aromatic cyclization of the product.

All the synthesized compounds were screened for antimicrobial (antibacterial, antifungal) activity and shown in table-2 & table-3. Among the compounds tested, compounds bearing X = 2- chloro (RJ-2d) , 4-chloro (RJ-2j), 2-nitro (RJ-2f) and 3-nitro (RJ-2 l) substituents showed very good antibacterial activity. Compounds bearing 4-methoxy (RJ-2 e),4 –hydroxy-3- methoxy – (eg:RJ-2k) &3,4,5 – trimethoxy (eg:RJ-2m) at X exhibited moderate to mild activity. Whereas, the all the remaining compounds exhibited least activity against all the bacterials. Fungicidal screening data also revealed similar pattern of activity, but the results were not encouraging. Only a few compounds imparted comparable fungicidal activity. Only the compounds bearing X = 2-chloro (RJ-2d), 4-chloro (RJ-2j) 2-nitro (RJ-2f) and 3-nitro (RJ-2 l) substituents showed better antifungal activity than the remaining compounds.

4. CONCLUSION

The title compounds 'RJ 2 a-m' were prepared from the starting compound 3- N-amino -2-methyl-5, 6-tetramethylene thieno [2, 3-d] - pyrimidin-4-one (**RJ2**) and were analyzed mainly by physical, TLC, IR, NMR and Mass spectral data. The compounds were screened for antibacterial and antifungal activity. Many of the synthesized compounds showed mild to moderate antimicrobial activity and some were equipotent to the standard employed. Finally it was observed that the synthesized compounds possessing 'electron withdrawing groups' on the aldehydic phenyl ring exhibited better antibacterial and antifungal activity compared to the compounds possessing 'electron donating groups**.**

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