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Synthesis and Antimicrobial Activity of Some Thiadiazolo Thienopyrimidines

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A series of compounds RP-2 to RP-9 were synthesized from 2-chloromethyl-1,3,4-thiadiazolo(2,3-b)6,7,8,9-tetrahydro-benzo(b)thieno(3,2-e)pyrimidin-5(4*H*)-one by refluxing with various substituted aromatic amine in dioxan using triethylamine as a catalyst. The IR and NMR spectra of the compounds were were investigated. All the compounds were screened for antibacterial activity against one gram-positive and one gram-negative bacteria.

Key Words: Synthesis, Thiadiazolothienopyrimidines, Antimicrobial, Substituted aromatic amines.

INTRODUCTION

Aromatic amine derivatives have shown to possess different pharmacological activities such as antimicrobial agents[1] and fungicidal activity[2]. Thienopyrimidinones are reported to possess antibacterial[3-9] and fungicidal activities[10-12]. While thiadiazolopyrimidinones have shown herbicidal[13], antitumour[14,15] and antiallergent activities[16,17]. Thiadiazoloquinazolines were prepared as biological analogs of purines. Thiadiazolo- and thienopyrimidines were prepared as the bioisosteres of thiadiazoloquinazo-lines[3]. In view of the importance of such compounds, it was felt worthwhile to complete the SAR studies of the thiadiazolothienopyrimidinones[18].

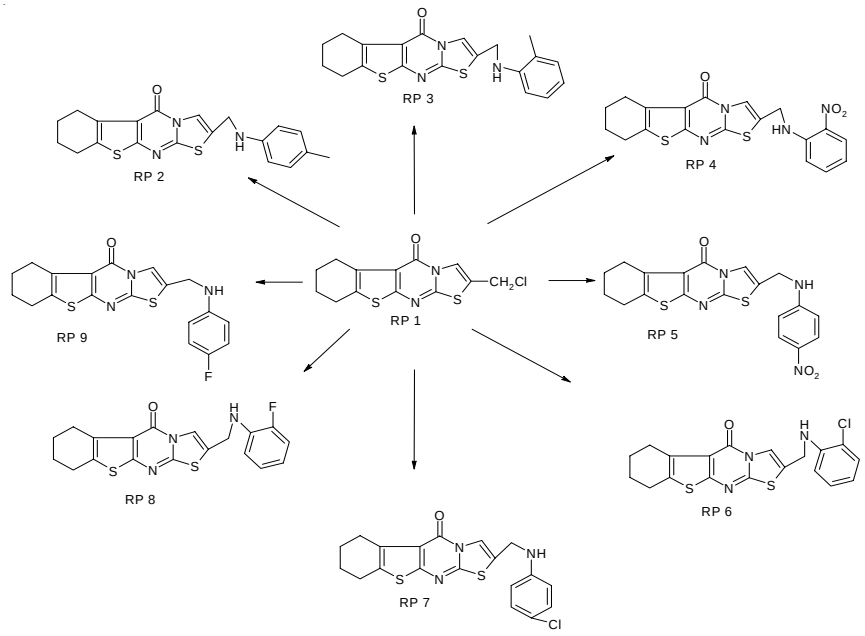
Herewith, the synthesis and the antibacterial activity of some novel 2-substituted-1,3,4-thiadiazolo(2,3-b)6,7,8,9-tetrahydrobenzo(b)thieno(3,2-e)pyrimidin-5(4*H*)-ones are reported.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The IR spectrum were run on Perkin Elmer FT-IR spectrophotometer (model no.-RX I) in KBr pellets. ^{1}H NMR was obtained using Jeol max 400 MHz in $CDCl_3$ solvent using TMS as internal reference.

All the solvents and chemicals were of analytical grade. Reagents and solvents were used without further purification.

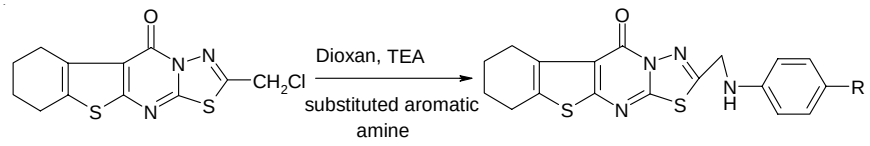
The synthesis of 2-substituted-1,3,4-thiadiazolo(2,3-b)6,7,8,9-tetrahydrobenzo(b)thieno(3,2-e)pyrimidin-5(4*H*)-ones is given here (**Scheme-I**). The spectral data are given in Table-1.



Scheme-I

General method for preparation of aromatic amine derivatives

(Preparation of 2-(*p*-toludinomethyl)1,3,4-thiadiazolo(2,3-b) 6,7,8,9-tetrahydrobenzo (b) thieno (3,2-e)pyrimidin-5-(4*H*)-one)[18]:



R = electron donating or electron withdrawing groups

A mixture of 2-chloromethyl-1,3,4-thiadiazolo(2,3-b)6,7,8,9-tetrahydrobenzo(b)thieno(3,2-e)pyrimidin-5(4*H*)-one (0.01 mol), triethylamine (0.01 mol) and substituted aromatic amines (0.01 mol) was subjected for reflux for 8 h. The reaction mixture was cooled to room temperature, poured into ice-cold water and excess amine neutralized with dilute HCl (10 %). The precipitate obtained was filtered, dried and recrystallized from alcohol[18-23].

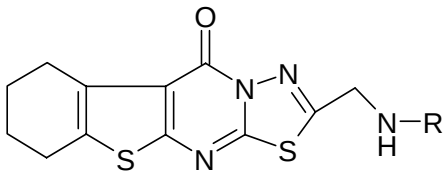
TABLE-1
SPECTRA DATA OF **RP2-RP9**

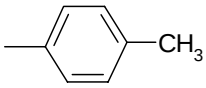
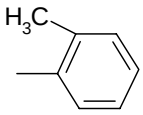
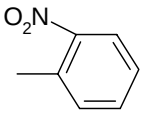
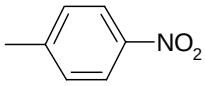
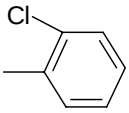
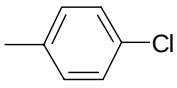
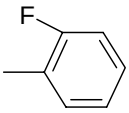
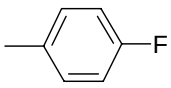
Compd. Name	NMR ($CDCl_3$, δ ppm)	IR (KBr, ν_{max}, cm^{-1})
RP2	–	3390 (-NH-), 1680 (-CO-), 2980 (aliphatic C-H), 3142 (aromatic C-H), 2840 (alkyl C-H)
RP3	δ = 7.07-7.13 (t, 1H, CH at 6'), 6.85-6.96 (t, 1H, CH, at 3'), 6.65-6.88 (d, 2H at 4' & 5`), 6.54-6.56 (d, 2H, CH_2 at 2), 3.27-3.32 (t, 2H, CH_2, at 9), 2.94-2.98 (t, 2H, CH_2 at 6), 2.41-2.44 (p, 2H,CH_2 at 8), 2.63-2.67 (t, 2H, CH_2 at 9), 1.81-1.94 (m, 4H, CH_2-CH_2 at 7 & 8)	3382 (-NH-), 1660 (-CO-), 2976 (aliphatic C-H), 3160 (aromatic C-H), 2870 (alkyl C-H)
RP4	–	3390 (-NH-), 1620 (-CO-), 2910 (aliphatic C-H), 3124 (aromatic C-H), 1470 (-NO_2-).
RP5	–	3410 (-NH-), 1592 (-CO-), 2910 (aliphatic C-H), 3124 (aromatic C-H), 1556 (-NO_2-).
RP6	δ = 7.69 (s, 1H, NH), 7.3-7.38 (d, 1H, CH at 3'), 7.15-7.17(d, 1H, CH at 6'), 6.98-7.12 (t, 1H, CH at 4'), 6.58-6.61 (t, 1H, CH at 5'), 2.63-2.67 (t, 2H, CH_2 at 8), 1.81-1.94(m, 4H, CH_2-CH_2 at 7 & 8) 1.56-162(t, 2H, CH_2 at 6) 1.20 (s, 2H, CH at 2)	1640 (C=O), 2851 (-C-H), 3290 (NH), 1647 (N=C-H), 1696 (Ar-C=C), 780 (C-Cl), 1556 (-NO_2-)
RP7	–	1680 (C=O), 2880 (-C-H), 3322 (NH), 1649 (N=C-H), 1680 (Ar-C=C), 765 (C-Cl)
RP8	–	1645 (C=O), 2960 (-C-H), 3360 (NH), 1612 (N=C-H), 1696 (Ar-C=C), 1190 (C-F)
RP9	–	1689 (C=O), 2951 (-C-H), 3390 (NH), 1610 (N=C-H), 1700 (Ar-C=C), 1170 (C-F)

Antimicrobial activity

The following compounds were screened for antimicrobial activity[24,25] against *E. coli* and *S. aureus*. The results are summarized in Table-2.

TABLE-2
ANTIMICROBIAL ACTIVITY OF **RP2-RP9**



Compound Name	R	*E. Coli*	*S. aureus*
RP 2		11	12
RP 3		9	9
RP 4		6	7
RP 5		4	7
RP 6		5	6
RP 7		5	3
RP 8		4	6
RP 9		5	5
Ampicillin	–	18	20

RESULTS AND DISCUSSION

The compounds RP2 to RP9 were synthesized from 2-chloromethyl-1,3,4-thiadiazolo(2,3-b)6,7,8,9-tetrahydrobenzo(b)thieno(3,2-e)pyrimidin-5(4*H*)-one by to refluxing with various substituted aromatic amine in dioxan using triethylamine as a catalyst.

The IR spectra of all the compounds and NMR spectra of RP 3 and RP 6 were taken, studied and the product formation was confirmed.

All the compounds were screened for antibacterial activity[25] against one gram-positive and one gram-negative bacteria using Ampicillin as the standard at 50 µg/mL concentration. compound. RP2 and RP3 were found to be more active antibacterial among the series and in case of electron donating group *para* substitution was found to be more effective than *ortho* substitution.

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