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Synthesis of 2-R 5-oxo5-H6- N-ethylcarboxamide7-phenyl-[1,3,4]thiadiazolo-[3,2-a]pyrimidine and 2-R 5-oxo5-H6- N-methylcarboxamide 7-phenyl-[1,3,4]thiadiazolo-[3,2-a]pyrimidine and Biological properties

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ABSTRACT: In this paperexplain preparation of 2-R 5-oxo5-H6-N-ethylcarboxamide 7-phenyl1,3,4-thiadiazolo-[3,2-a] pyrimidine and 2-R 5-oxo 5-H 6 -N-methyl carboxamide 7-phenyl 1,3,4-thiadiazolo-[3,2-a] pyrimidine through reaction of 2-R 5-Oxo5-H 6- ethylcarboxilate 7 - phenyl -1, 3,4 -thiadiazolo-[3,2-a] pyrimidine with N-ethylamine and N-methylamine. Interest in the synthesis of pyrimidine derivatives is due to their biological activities. These compounds have many medicinal properties and are used in allergy.

Keywords: Pyrimidine, N-ethylcarboxamide-N-methylcarboxamide, Medicinal properties, Synthesis, Spectroscopy.

INTRODUCTION

Condensed derivatives of 1,3,4-thiadiazolo-[3,2-a]pyrimidine were reported to possess a broadspectrum of biological activity [1–4], including antibacterial, antitumor, fungicidal, and herbicidal properties. However, thiadiazoles and their condensed analogs are still insufficiently studied. In continuation of the search for substances possessing increased ability to permeate through biological membranes of various infectious species [5–7] and, in particular, for the new antibacterial drugs in these homologousseries of compounds.

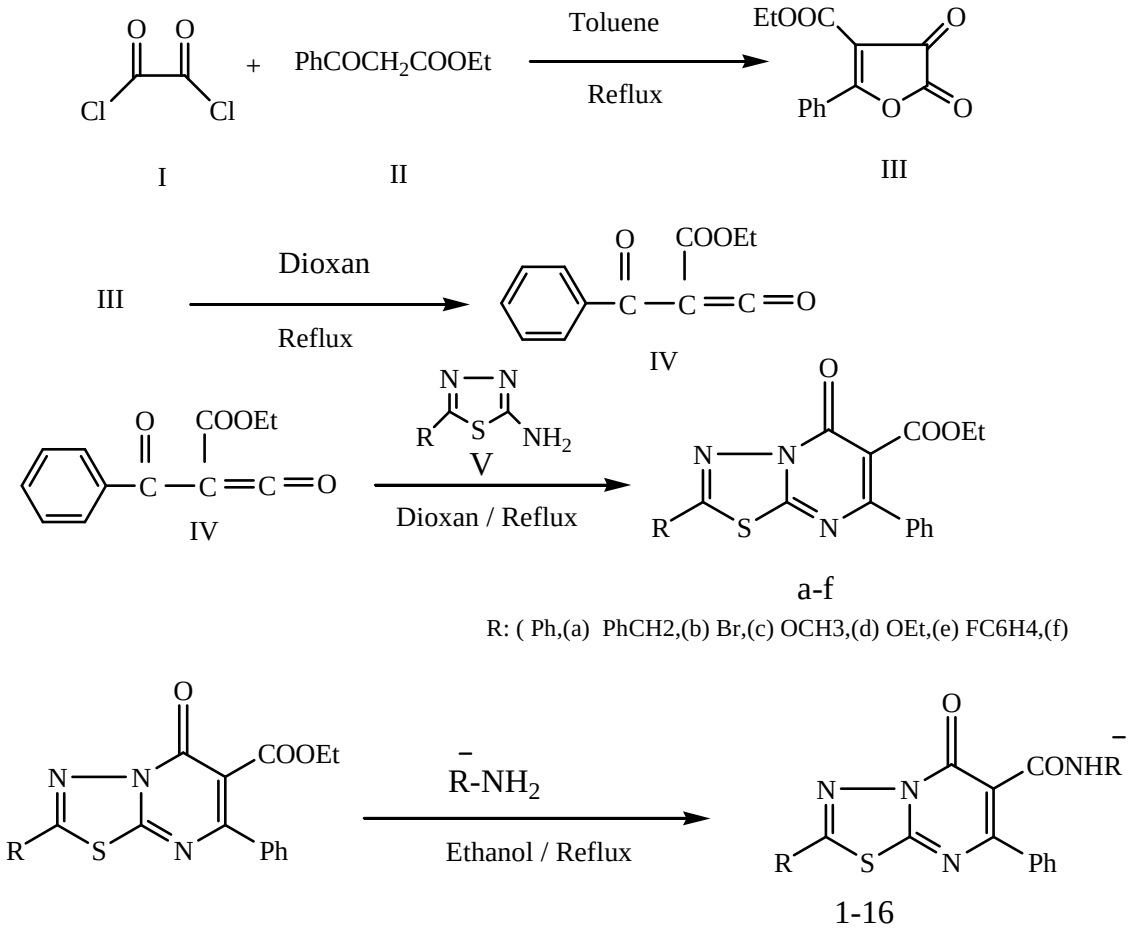
1,3,4-thiadiazolo [3,2-a] pyrimidine system efficientlyenhances the physiological activity of the molecule[8-10].

This replacement occurs in the reactions of 1,3,4-thiadiazolo [3,2-a] pyrimidine derivatives with electrophiles [11,12].at position 6 of the

Literature data on fused heterocycles with a thiadiazolo-[3,2-a] pyrimidine system anrelated with anotherring are scarce. These include 1,3,4-thiadiazolo -[2,3 -b] quinozalines,[13-15] pyrazolo[3 ,4-e]1,3,4-thiadiazolo-[3,2-a] pyrimidines, [16] and 1,3,4-thiadiazolo-[3 ,2-a] pyrido [3,2-e] pyrimidines [17].

Derivatives of 1,3,4-thiadiazolo-[3,2-a] pyrimidine are potential biologically active substances [18-26]. The introduction of ketene dithioacetal fragments into the molecules makes it possible to synthesize heterocyclic systems with various functional groups [27, 28].

We Synthesis 2-R 5-oxo 5-H 6 -N-ethylcarboxamide, N-methylcarboxamide7-phenyl 1,3,4-thiadiazolo-[3,2-a] Pyrimidine in multi-stage (Scheme 1).

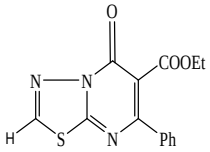
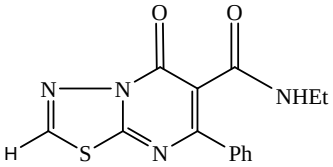
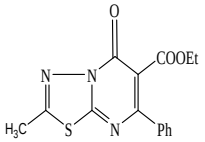
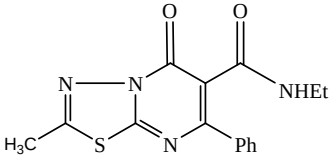
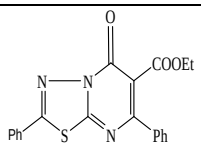
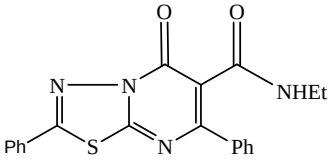
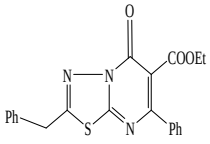
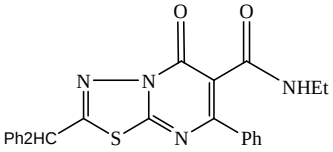
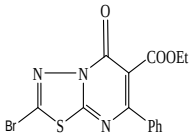
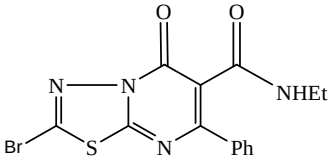
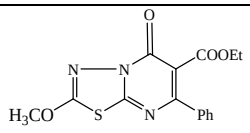
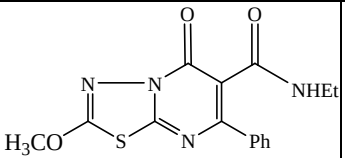
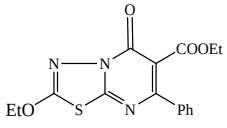
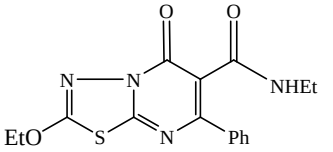
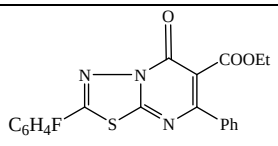
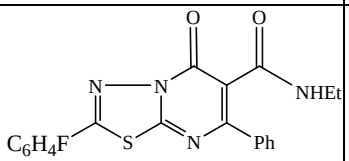


Scheme 1: Synthesis of 2-R 5-Oxo 5-H 6-R-amide derivatives 7-phenyl -1,3,4-thiadiazolo-[3,2-a]- pyrimidine.

RESULTS AND DISCUSSION

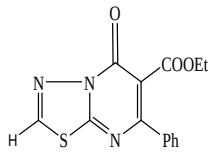
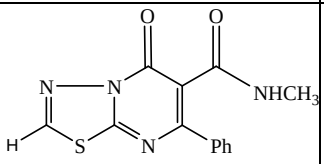
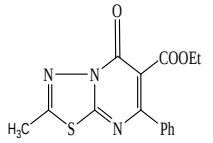
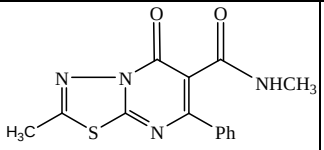
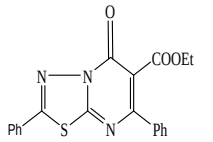
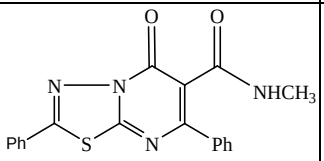
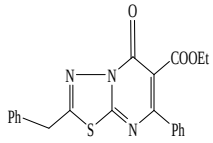
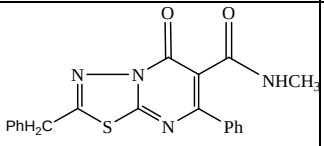
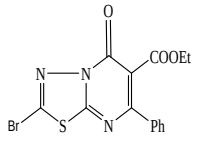
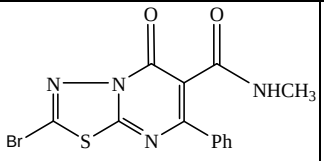
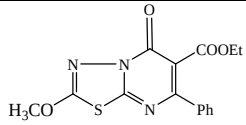
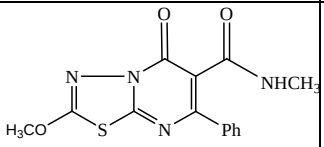
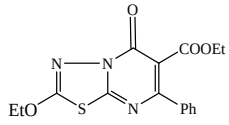
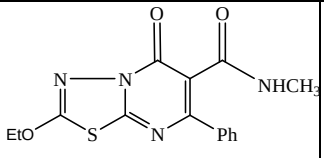
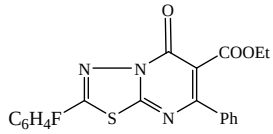
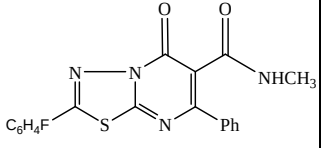
we synthesized of 2-R5-oxo5-H6-N-ethylcarboxamide,N-methylcarboxamide7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine from 2-R5-oxo5-H 6-ethylcarboxylate 7-phenyl1,3,4-thiadiazolo[3,2-a] pyrimidine and N-ethylamine and N-methylamine in various solvent. But alcohols are the best solvents to this reaction. The alcohols such asmethanolandethanolalcohol have moreuse. This compounds (2- R5-oxo5-H6-N-ethylcarboxamide, N-methylcarboxamide7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine) can be useful in the search for new antimicrobial drugs. The antimicrobial activity of thiadiazolo pyrimidine (1-16) was studied with respect to a series of test microbes. The antibacterial activity was evaluated by broth micro dilution susceptibility tests as recommended by clinical laboratory standard institute (CLSI) for determination of the minimum concentration of samples required for inhibition of visible growth of bacteria. The data obtained show that compounds 2-R5-oxo5-H6-N-ethylcarboxamide, N-methylcarboxamide7-phenyl-1,3,4-thiadiazolo [3,2-a] pyrimidine, have antimicrobial *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli* and etc.

Table 1: Synthesis of 2- R 5-oxo 5-H 6-N-ethylcarboxamide7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine from 2- R 5-oxo 5-H 6-ethylcarboxylate 7-phenyl 1 ,3,4- thiadiazolo [3,2-a] pyrimidine and N-ethylamin [a].

Entry	Thiadiazol pyrimidine	N-ethylamin	Product	Time(h)	Yield[b] (%)	Melting point
7		NH_2Et		7	85	155-156
8		NH_2Et		5	92	163-165
9		NH_2Et		6	95	170-171
10		NH_2Et		6	88	155-157
11		NH_2Et		7	85	173-174
12		NH_2Et		6	85	161-163
13		NH_2Et		6	87	168-170
14		NH_2Et		5	90	175-176

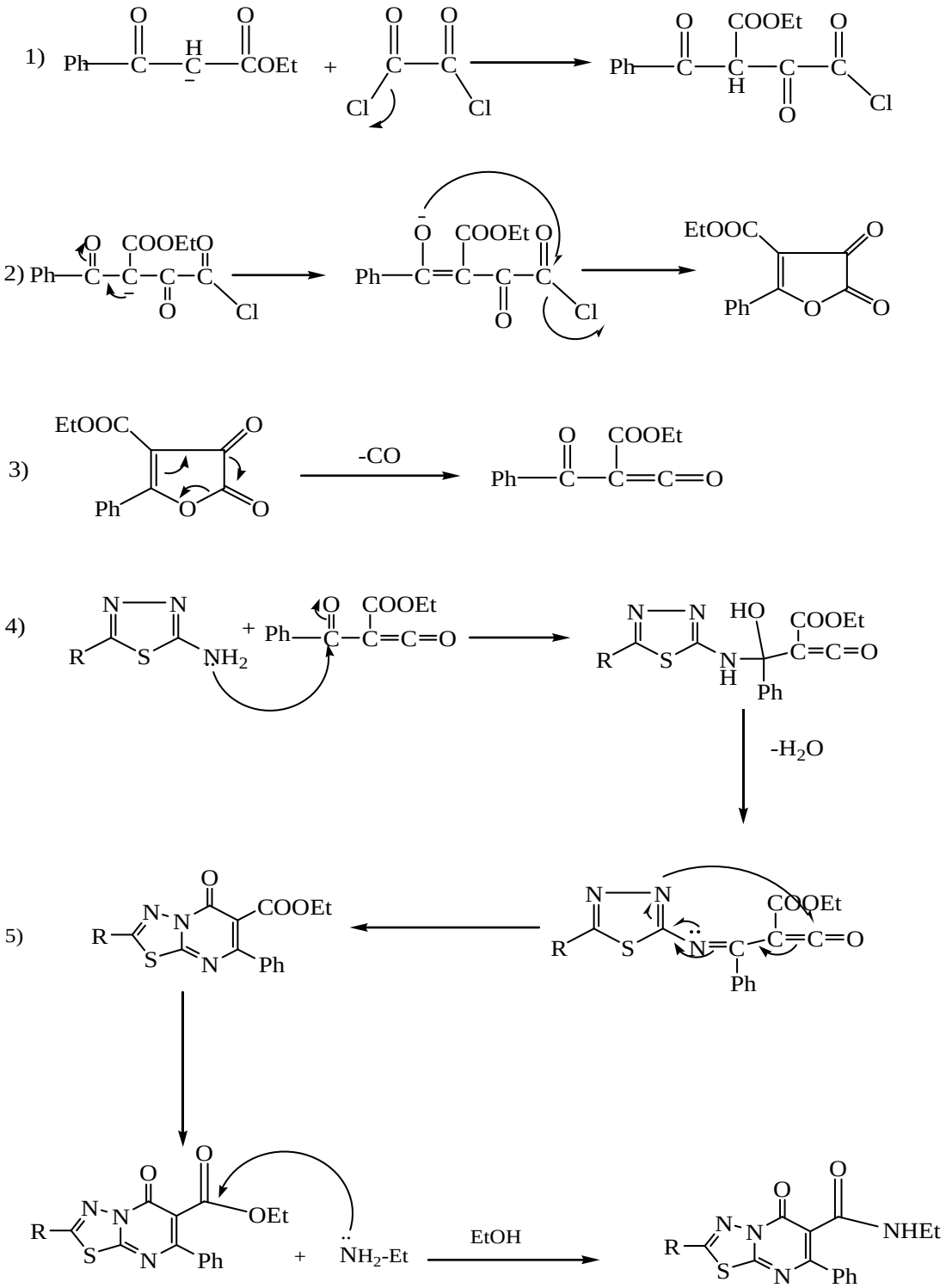
[a] Reactions were carried out with 2- R 5-oxo 5-H 6-ethylcarboxylate 7-phenyl 1 ,3,4- thiadiazolo-[3,2-a] pyrimidine and N-ethylamin
[b] Yields refer to isolated pure products

Table 2. Synthesis of 2- R 5-oxo 5-H 6-N-methylcarboxamide7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine from 2- R 5-oxo 5-H 6-ethylcarboxylate 7-phenyl 1 ,3,4- thiadiazolo [3,2-a] pyrimidine and N-methylcarboxamide [a].

Entry	Thiadiazol pyrimidine	N-methylamin	Product	Time(h)	Yield[b](%)	Melting point
15		NH_2-CH_3		11	82	145-147
16		NH_2-CH_3		8	86	158-160
17		NH_2-CH_3		7	90	166-168
18		NH_2-CH_3		8	88	164-166
19		NH_2-CH_3		8	85	170-171
20		NH_2-CH_3		7	92	163-165
21		NH_2-CH_3		9	80	162-164
22		NH_2-CH_3		7	90	173-175

[a]Reactions were carried out with 2- R 5-oxo 5-H 6-ethylcarboxylate 7-phenyl 1 ,3,4- thiadiazolo-[3,2-a] pyrimidine and N-methylamin,
[b]Yields refer to isolated pure products

To show the generality and applicability of this procedure, we treated a wide variety of 2- R 5-oxo 5-H 6-ethylcarboxylate 7-phenyl 1,3,4- thiadiazolo [3,2-a] pyrimidine and N-ethylaminandN-methylaminin the presence of alcohol ethanol at 78°C and obtained the desirable products in good to excellent yields (Table 1,2).



Scheme 2. Mechanism of reaction for Synthesis of 2-Benzyl 5-Oxo 5-H 6-R-amide derivatives 7-phenyl -1,3,4-thiadiazolo-[3,2-a]- pyrimidine.

EXPERIMENTAL

For the synthesis 2-R 5-oxo 5-H 6-N-ethylcarboxamide 7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine. For example, for the synthesis 2-Ph 5-oxo 5-H 6-N-ethylcarboxamide 7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine, first: oxalic acid dichloride (1,0.127g) and ethyl benzoylacetate (0.86mmol,0.165g) reacted together in toluene at $110^{°C}$ until is produced ethyl-4,5-dioxo-2-phenyl-4,5-dihydrofuran-3-carboxylate(0.23g,92%) and in another stage ethyl-4,5-dioxo-2-phenyl-4,5-dihydrofuran-3-carboxylate (1mmol,0.25g) in boiling dioxan converted to ethyl-2-formyl-3-oxo-3-phenyl propanoate (that isanopen cycle).

At more mixture of 2-Ph5-amino-1,3,4-thiadiazole (1mmol, 0.177g), ethyl-2-formyl-3-oxo-3-phenylpropanoate (1mmol,0.218g) was stirred magnetically in toluene at 110^{oC}for10-14 hours(12h) and the progress of the reaction was monitored by thin-layer chromatography (TLC). The reaction mixture was filtered. In all the cases, the product 2-Ph5-oxo 5-H 6-ethylcarboxylate 7-phenyl 1,3,4- thiadiazolo- [3,2-*a*]-pyrimidine obtained (85%,0.332g) .

A mixture of 2-Ph 5-oxo 5-H 6-ethylcarboxylate 7-phenyl 1,3,4- thiadiazolo [3,2-a] pyrimidine (1 mmol,0.391g) and N-ethylamin (1 mmol,0.045g) was stirred magnetically at 78^{o}C and the progress of the reaction was monitored by thin-layer chromatography (TLC). The reaction mixture was filtered .The product obtained after the usual work up gave satisfactory spectral data. And the production obtained in (0.357g, 95% yield).

A. Spectral data

1)-**2-H 5-oxo 5-H 6-N-ethylcarboxamide 7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine**:^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.2(t,3H,CH_3);3.1(q,2H,CH_2) ;7.15-7.40 (5H, Ph);7.55(s, H,CH);8.2(1H,NH); - ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):15.1(CH_3), 34.2(CH_2), 118 (C), 126,4 (CH) , 126,4 (CH) ,128(CH), 128.7(CH), 128.7(CH), 136.9(C), 140.4(CH), 159 .8(C),162.1(C), 163 (C),168(C).

2)-**2-CH_3 5-oxo 5-H 6-N-ethylcarboxamide 7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine**:^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.9(s,3H,CH_3); 1.2(t,3H,CH_3);3(q,2H,CH_2) ;7.30-7.46 (5H, Ph);8.2(1H,NH); - ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):15(CH_3), 24.2(CH_3), 34(CH_2),118 (C), 126,4 (CH) , 126,4 (CH) ,128(CH), 128.7(CH), 128.7(CH), 136.9(C), 154.7(C), 159 .8(C), 162.1(C), 163 (C), 168(C).

3)-**2-Ph 5-oxo 5-H 6-N-ethylcarboxamide 7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine**:^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.3(t,3H,CH_3);3.2(q,2H,CH_2); 7.30-7.50 (10H, 2Ph);8.3(1H,NH); - ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):15.1(CH_3), 34.1(CH_2), 118 (C), 126,4 (CH), 126,4 (CH) ,128(CH), 128.7(CH), 128.7(CH), 128.9(CH), 128.9(CH), 129.2(CH),129.2(CH), 130.7(C), 136.9(C), 143.7(C), 159 .8(C), 162.1(C), 163 (C),168(C).

4)-**2-PhCH_2 5-oxo 5-H 6-N-ethylcarboxamide 7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine**:^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.2(t,3H,CH_3); 2.6(s,2H,CH_2); 3(q,2H,CH_2) ;7.07-7.50 (10H,2Ph);8.1(1H,NH); - ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):15(CH_3), 34.2(CH_3), 38.2(CH_2),118 (C),125,8 (CH) , 126,4 (CH) , 126,4 (CH) ,128(CH), 128.7(CH), 128.7(CH),128.7(CH),128.7(CH), 129.1(CH),129.1(CH), 136.9(C),137.5(C),145.6(C), 159 .8(C),162.1(C), 163 (C),168(C).

5)-**2-Br 5-oxo 5-H 6-N-ethylcarboxamide 7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine**:^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.2(t,3H,CH_3);3(q,2H,CH_2) ; 7.14-7.30 (5H, Ph);8.1(1H,NH); - ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):15(CH_3), 34(CH_2),118 (C), 126,4 (CH) , 126,4 (CH) ,128(CH), 128.7(CH), 128.7(CH), 136.9(C), 154.7(C), 159 .8(C), 162.1(C), 163 (C),168(C).

6)-**2-CH_3O 5-Oxo 5-H 6-N-ethylcarboxamide 7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine**:^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.2(t,3H,CH_3);3(q,2H,CH_2) 3.3(s,3H,CH_3);7.14-7.35 (5H, Ph);8.2(1H,NH); - ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):15(CH_3), 34.2(CH_2), 47.7(CH_3),118 (C), 126,4 (CH) , 126,4 (CH),128(CH), 128.7(CH), 128.7(CH), 136.9(C), 154.7(C), 159 .8(C), 162.1(C), 163 (C),168(C).

7)-**2-EtO 5-Oxo 5-H 6-N-ethylcarboxamide 7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine**: ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.01(t,3H,CH_3); 1.2(t,3H,CH_3);3(q,2H,CH_2) ;3.4(q,2H,CH_2); 7.15-7.30 (5H, Ph);8.2(1H,NH); - ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):14.6(CH_3), 15.1(CH_3), 34.2(CH_3), 57.3(CH_2),118 (C), 126,4 (CH), 126,4 (CH) ,128(CH), 128.7(CH), 128.7(CH), 136.9(C), 154.7(C), 159 .8(C), 162.1(C), 163 (C),168(C).

8)-**2-C_6H_4F 5-Oxo 5-H 6-N-ethylcarboxamide 7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine**:^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.2(t,3H,CH_3);3(q,2H,CH_2) ;7.15-7.65 (10H,2Ph);8.1(1H,NH); - ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):15.1(CH_3), 34.2(CH_2),115.6 (CH),115.6 (CH), 118 (C), 126,4 (CH) , 126,4 (CH) ,128(CH), 128.7(CH), 128.7(CH), 130.8(CH), 130.8(CH), 136.9(C),143.8(C),159 .8(C), 162.1(C), 163 (C),165.2(C),168(C).

9)-**2-H 5-oxo 5-H 6-N-Methylcarboxamide 7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine**:^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.7(s,3H,CH_3);7.15-7.40 (5H, Ph);7.55(s, H,CH);8.2(1H,NH); - ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):26.1(CH_3), 118 (C), 126,4 (CH) , 126,4 (CH) ,128(CH), 128.7(CH), 128.7(CH), 136.9(C), 140.4(CH), 159 .8(C),162.1(C), 163 (C),168(C).

10)-**2-CH_3 5-oxo 5-H 6-N-Methylcarboxamide 7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine**:^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.9(s,3H,CH_3); 2.7(s,3H,CH_3); 7.30-7.46 (5H, Ph);8.1(1H,NH); - ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):24.2(CH_3), 26.3(CH_3), 118 (C), 126,4 (CH) , 126,4 (CH) ,128(CH), 128.7(CH), 128.7(CH), 136.9(C), 154.7(C), 159 .8(C),162.1(C), 163 (C),168(C).

11)-**2-Ph 5-oxo 5-H 6-N-Methylcarboxamide 7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine**:^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.7(s,3H,CH_3);;7.15-7.6 (10H, 2Ph);8.2(1H,NH); - ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 26.3 (CH_3),118 (C), 126,4 (CH) , 126,4 (CH) ,128(CH), 128.7(CH), 128.7(CH), 128.9(CH), 128.9(CH), 129.2(CH),129.2(CH), 130.7(C),131.1(C), 136.9(C), 143.7(C), 159 .8(C),162.1(C), 163 (C),168(C).

12)-**2-PhCH_2 5-oxo 5-H 6-N-Methylcarboxamide 7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine**:^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.6(s,2H,CH_2);2.7(s,3H,CH_3) ;7.14-7.65 (10H,2Ph);8.1(1H,NH); - ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):26.3(CH_3), 38.2(CH_2),118 (C),125,8 (CH) , 126,4 (CH) , 126,4 (CH) ,128(CH), 128.7(CH), 128.7(CH),128.7(CH),128.7(CH), 129.1(CH),129.1(CH), 136.9(C),137.5(C), 145.8(C), 159 .8(C),162.1(C), 163 (C),168(C).

13)-**2-Br 5-oxo 5-H 6-N-Methylcarboxamide 7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine**:^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.7(s,3H,CH_3); 7.14-7.30 (5H, Ph);8.1(1H,NH); - ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 26.3(CH_3),118 (C), 126,4 (CH) , 126,4 (CH) ,128(CH), 128.7(CH), 128.7(CH), 136.9(C), 154.7(C), 159 .8(C),162.1(C), 163 (C),168(C).

14)-**2-CH_3O 5-Oxo 5-H 6-N-Methylcarboxamide 7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine**:^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):2.7(s,3H,CH_3);3.4(s,3H,CH_3) 7.14-7.35 (5H, Ph);8.2(1H,NH); - ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):26.2(CH_3), 47.7(CH_3),118 (C), 126,4 (CH) , 126,4 (CH) ,128(CH), 128.7(CH), 128.7(CH), 136.9(C), 154.7(C), 159 .8(C),162.1(C), 163 (C),168(C).

15)-**2-EtO 5-Oxo 5-H 6-N-Methylcarboxamide 7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine**:^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.01(t,3H,CH_3); 2.75(s,3H,CH_3) ;3.4(q,2H,CH_2);7.15-7.30 (5H, Ph);8.2(1H,NH); - ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):14.6(CH_3), 26.3(CH_3), 57.3(CH_2),118 (C), 126,4 (CH) , 126,4 (CH) ,128(CH), 128.7(CH), 128.7(CH), 136.9(C), 154.7(C), 159 .8(C),162.1(C), 163 (C),168(C).

16)-**2-C_6H_4F 5-Oxo 5-H 6-N-Methylcarboxamide 7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine**:^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.7(s,3H,CH_3); 7.15-7.65 (10H,2Ph);8.1(1H,NH); - ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):26.3(CH_3), 115.6 (CH),115.6 (CH), 118 (C), 126,4 (CH) , 126,4 (CH) ,128(CH), 128.7(CH), 128.7(CH), 130.8(CH), 130.8(CH), 136.9(C),143.8(C),159 .8(C),162.1(C), 163 (C),165.2(C),168(C).

CONCLUSIONS

In the present work, we design and discover a new class of2- R 5-oxo 5-H 6- N-methylcarboxamide7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine and 2- R 5-oxo 5-H 6-N-ethylcarboxamide7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine. The preliminary results showed that most of this synthesis ,variousalcohol have been employed as a mild and highly efficient solvent system for the convenient preparation of 2-R 5-oxo 5-H 6- N-methylcarboxamide7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine and 2-R 5-oxo 5-H 6-N-ethylcarboxamide7-phenyl -1,3,4-thiadiazolo [3,2-a] pyrimidine in excellent yields from 2-R 5-Oxo 5-H 6-ethylcarboxylate 7-phenyl 1,3,4- thiadiazolo-[3,2-a]-pyrimidine and N-ethylaminand N-methylamin. The advantages include low cost, mild reaction conditions and with excellent yields.

The antimicrobial activity of 2-R5-Oxo 5-H 6-Amide derivatives7-phenyl 1,3,4- thiadiazolo- [3,2-a]-pyrimidine (1-16) was studied with respect to a series of test microbes.

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