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# SYNTHESIS AND CHARACTERIZATION OF NEW PYRIMIDINE DERIVATIVES AND STUDY OF THEIR ANTIMICROBIAL ACTIVITY

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**Abstract**

Pyrimidine derivative (1) is prepared through the reaction of 4-oxo-4-biphenylbut-2-enoic acid and thiourea. Reaction of 1 with ethyl chloroacetate afforded the corresponding pyrimidine ester (II) which is converted to the arylidenes (III & IV) and hydrazine derivative (V). The behaviour of the obtained hydrazine was studied towards sodium nitrite/HCl, 3.4.5-trimethoxybenzaldehyde and acetone. Reaction of pyrimidine derivative 1 with acetyl chloride gave the N-acetyl derivative (X), which is converted to the pyrimidine-pyridone derivative (XI). The enol form of the pyridone ring is used in the preparation of the chloro derivative (XII). The reaction of the chloro derivative with sodium azide, amines, hydrazine hydrate and benzenesulfanilamide derivatives have also been taken into consideration. The in-vitro anti-bacterial screening revealed that some of the new compounds possess activity against Gram-positive, Gram-negative bacteria and fungi.

## Introduction:

Due to the interesting activity of pyrimidine derivatives as biological agents considerable attention has been focused on this class. Pyrimidines exhibit antitumar[1], antimycobacterial[2], antiviral[3], anticancer[4], antiinflammatory[4,5], analgesic[4,5], antifolate[6], antimicrobial[7], antifungal[8], antiproliferative[9] and antihestaminic[10].

They are also effective as antiplatelet agents with analgesic activity[11] and as a new drug for treatment of insomnia[12]. This prompted the author to use 6-(4-biphenyl)-2-thioxo-2,3,4,5-tetrahydropyrimidine-4-carboxylic acid (I) as key intermediate in the synthesis of some new pyrimidine derivatives. IR spectrum of I showed bands at 1700, 1222 and 3244 $cm^{-1}$ for C=O (acid), C=S and NH.

When (I), was allowed to react with ethyl chloroacetate in acetone in the presence of anhydrous potassium carbonate, 6-(4-biphenyl)-2-[2(ethoxycarbonyl) methyl thio]-4,5-dihydro-pyrimidine-4-carboxylic acid (II) was obtained.

The structure of II was derived from the IR spectrum which showed bands at 1732, 1710 and1602 $cm^{-1}$ for C=O (ester), C=O (acid) and C=N respectively.

The structure of II was further supported by its reaction with benzaldehyde in hot ethanol in the presence of sodium ethoxide to give 2-{[1-hydroxy carboxy-2-phenyl vinyl]thio}-6-(4-biphenyl)-4,5-dihydropyrimidine-4-carboxylic acid (III) and 2-{[1-(ethoxycarbonyl)-2-phenylvinyl]thio}-6-(4-biphenyl)-4,5-dihydropyrimidine-4-carboxylic acid (IV). The IR spectrum of III showed bands at 1726 and 1598 $cm^{-1}$ for C=O (acid) and C=N, while that of (IV) showed bands at 1759, 1700 and 1620 $cm^{-1}$ for C=O (ester), C=O (acid) and C=N , respectively.

On the other hand, reaction of II with hydrazine hydrate in boiling ethanol gave 6-(4-biphenyl)-2[(2-hydrazino-carbonyl-methyl) thio]-4,5-dihydropyrimidine-4-carboxylic acid (V). Its IR spectrum showed bands at 1700, 1668, 1596, 3358, 3206 for C=O (acid), C=O amide, C=N, NH and $NH_2$.

The resulting hydrazide derivative V has been used as starting material for the preparation of a series of new compounds. Thus, reaction of V with sodium nitrite and dilute HCl at $0^oC$ gave 6-(4-biphenyl)-2-{(2-oxo-2(1H-triaziren-1-yl)ethyl] thio}-4,5-dihydropyrimidine-4-carboxylic acid (VI). Its IR spectrum showed bands at 1700, 1662, 1612 $cm^{-1}$ for C=O (acid), C=O and C=N.

Surprisingly, repeating the reaction with sodium nitrite and conc. HCl at 10 $^oC$ the resulting product was 8-(4-biphenyl)-3-oxo, 3,4-dihydro-2H, 9a-H-pyrimido[2,1-b][1,3,4]thiodiazine-6-carboxylic acid (VII). Its IR spectrum showed bands at 1700, 1659, 1639 $cm^{-1}$ for C=O (acid), C=O and C=N.

Condensation of V with 3,4,5-trimethoxy benzaldehyde in boiling ethanol gave 2-{[3-oxo-5-(3,4,5-trimethoxyphenyl)pyrazolidin-4-yl] thio}-6-(4-biphenyl)-4,5-dihydropyrimidine-4-carboxylicacid (VIII). Its IR spectrum showed bands at 1700, 1668, 1614 $cm^{-1}$ for C=O (acid), C=O and C=N.

While, reaction of V with acetone gave 2-[(3,3-dimethyl-5-oxo pyrazolidine-4-yl)thio]-6-(4-biphenyl)-4,5-dihydropyrimidine-4-carboxylicacid(IX). Its IR spectrum showed bands at 1700, 1684, 1598 and 3062 $cm^{-1}$ for C=O (acid), C=O, C=N and NH.

The mass spectrum of compound IX shows the parent ion peak at m/z 422 (9.9%), the base peak at 77 (100%) and other significant peaks appeared at 421 (10.3%), 335 (11.9%), 248 (56.6%), 191 (62.0%), 115(18.9%) and 55(5.6%).

Interestingly, when compound 1 was allowed to react with acetyl chloride, 3-acetyl-6-(4-biphenyl)-2-thioxo-2,3,4,5-tetrahydropyrimidine-4-carboxylic acid (X), was obtained. Its IR spectrum sowed bands at 1710, 1679, 1601 $cm^{-1}$ for C=O (acid), C=O and C=N.

Reaction of X with ethyl 2-cyano-3-(4-methoxyphenyl)acrylate in the presence of ammonium acetate gave 3-[s-cyano-4-(4-methoxyphenyl)-6-oxo-1,4,5,6-tetrahydropyridine-2-yl)-2-thioxo-6-(4-biphenyl)-2,3,4,5-tetrahydropyrimidine-4-carboxylicacid (XI). Its IR spectrum showed bands at 1716, 1678, 1585, 3200 $cm^{-1}$ for C=O (acid), C=O, C=N and NH.

The behaviour of the pyrimidine derivative XI towards electrophilic reagents like $POCl_3$ has also been investigated. Treatment of XI with a mixture of phosphorus oxychloride and phosphoruspentachloride gave 3-[6-chloro-5-cyano-4-(4-methoxyphenyl)-pyridin-2-yl]-2-thioxo-6-(4-biphenyl)2,3,4,5-tetrahydro pyrimidine-4-carboxylic acid XII. Its IR spectrum showed bands at 1760, 1585, 2214 $cm^{-1}$ for C=O (acid), C=N and C≡N.

The mass spectrum of compound XII shows the parent ion peak at m/z 552 (0.84%) and the base peak at 181 (100%) and other significant peaks appeared at 429 (1.0%), 388 (1.78%), 346 (28.75%), 276 (22.21%), 200 (10.94%), 152 (66.05%), 77 (37.91%) and 60 (15.49%).

Structure of XII was further supported by the following reactions. Thus, reaction of XII with sodium azide in acetic acid gave 3-[8-cyano-7-(4-methoxyphenyl) tetrazolo[1,5-a]pyridine-5-yl]-2-thioxo-6-(4-biphenyl)-2,3,4,5-tetrahydropyrimidine-4-carboxylic acid XIII. Its IR spectrum showed bands at 1700, 1596, 2214 $cm^{-1}$ for C=O (acid), C=N and C≡N.

When XII was allowed to react with 2-aminopyridine, n-propylamine, p-nitroaniline and hydrazine hydrate, 3-[5-cyano-4-(4-methoxyphenyl)-6-(pyridine-2-yl-amino)-pyridin-2-yl]-2-thioxo-6-(4-biphenyl)-2,3,4,5-tetrahydropyrimidine-4-carb-oxylicacid (XIVa), 3-[5-cyano-4-(4-methoxyphenyl)-6-(propylamino)pyridine-2-yl]-2-thioxo-6-(4-biphenyl)-2,3,4,5-tetrahydropyrimidine-4-carboxylic acid (XIVb), 3-[5-cyano-4-(4-methoxyphenyl)-6-[(4-nitro-phenyl)amino] pyridine-2-yl]-2-thioxo-6-(4-biphenyl)-2,3,4,5-tetrahydropyrimidine-4-carboxylic acid (XIVc) and 3-[5-cyano-4-(4-methoxyphenyl)-6-hydrazinopyridin-2-yl]-2-thioxo-6-(4-biphenyl)-2,3,4,5 tetrahyropyrimidine-4-carboxylicacid (XIVd), were obtained respectively. Their IR spectra showed bands at 1712-1700, 1612-1600, 2221-2214 $cm^{-1}$ for C=O (acid), C=N and C≡N.

Reaction of XII with 4-amino-N-(5-methyl isoxazol-3-yl)benzene-sulfonamide, 4-amino-N-(4,6-dimethylpyrimidin-2-yl)benzenesulfonamide and 4-amino-N-[amino(imino)methyl]benzenesulfonamide gave 3-(6-{[4-({[5-methyliso-xazol-3-yl]amino}sulfonyl)phenyl]amino}-5-cyano-4-(4-methoxyphenyl)pyridine-2-yl)-6-(4-biphenyl)-2-thioxo-2,3,4,5-tetrahydropyrimidine-4carboxylic acid (XVa), 3-

(6-{[4-({[4,6-dimethylpyrimidin-2-yl]amino}sulfonyl)phenyl]amino}-5-cyano-4-(4-methoxyphenyl)pyridine-2-yl)-6-(4-biphenyl)-2-thioxo-2,3,4,5tetrahydropyrimidine-4-carboxylic acid (XVb) and 3-(6-{[4-({[amino-imino)methyl] amino}sulfonyl) phenyl]amino}-5-cyano-4-(4-methoxyphenyl)pyridine-2-yl)-6-(4-biphenyl)-2-thioxo-2,3,4,5-tetrahydropyrimidine-4-carboxylic acid (XVc), respectively. Their IR spectra showed bands at 1710, 1598-1597 and 2220-2214 $cm^{-1}$ for C=O (acid), C=N and C≡N.

The mass spectrum of compound XVa shows the parent ion peak at m/z 767 (5.69%) and the base peak at m/z 80 (40%) and other significant peaks appeared at 472 (9.00%), 451 (12.32%), 360 (11.85%), 234 (18.96%), 185 (29.38%) and 101 (30.33%).

***Screening for antimicrobial activity***

In this study the activity of the prepared compounds (III, IV, V, VII, VIII, IX, X, XI, XII, XIII, XIVa, XVa, XVb and XVc) was tested by the disc diffusion method the zones of inhibition were listed in (Table 3).

From (Table 3), it is clear that, the tested compounds (IV, V, VII, IX, X, XI, XII, XIII, XVa, XVb and XVc) possessed high activity against Gram positive while tested compounds (III, VIII and XIVa) possessed moderate activity.

All compounds possessed high activity against Gram negative except (III) possessed moderate activity.

All compounds possessed high activity against fungi except (IX, XIII, XIVa and XVc) possessed moderate activity while compounds (III and VIII) possessed less activity.

**Experimental**

All melting points are uncorrected. Elemental analyses were carried out in the Micro analytical Center, Cairo University, Giza. A.R. Egypt. IR spectra (KBr) were recorded on a FTIR 8201 PC Chimadzu (Japan, 1995) and $^{1}$H-NMR spectra recorded on a Varian 300 MHz (Germany 1999) using TMS as Internal Standard Chemical Shifts were expressed in δ ppm. EIMS were recorded on a mass GCMSQP 1000 PX Shimadzu (Japan 1990), physico, chemical and spectral properties of the prepared compounds are listed in (Tables 1,2).

***Formation of 6-(4-biphenyl)-2-thioxy-2,3,4,5-tetrahydro pyrimidine-4-carboxylic acid (I).***

A mixture of 4-biphenyl-4-oxo-2-butenoic acid (0.01 mol; 2.52 g) and thiourea (0.01 mol; 0.76 g) in ethanol/acetic acid mixture (25 : 30 ml) was refluxed for 6

hours. After concentration and cooling the product was poured onto water and the solid that formed filtered, washed well with water and dried to give I.

***Formation of 6 (4-biphenyl)-2-[(2-ethoxycarbonyl methyl) thio]- 4,5-dihydro pyrimidine-4-carboxylic acid (II).***

A mixture of I (0.01 mol; 2.92 g) and ethyl chloroacetate (0.015 mol : 1.87 g) in dry acetone (50 ml) containing anhydrous potassium carbonate (0.04 mol : 5 g) was refluxed on a steam bath for 24 hours after concentration and cooling the reaction mixture was poured onto water and the solid that separated to give II.

***Formation of 2-{[1-hydroxycarboxy-2-phenyl vinyl]thio}-6-(4-biphenyl) 4,5-dihydropyrimidine-4-carboxylicacid (III) and 2-{[1-(ethoxy-carbonyl)-2-phenyl] thio}-6-(4-biphenyl)-4,5-dihydroprimidine-4-carboxylic acid (IV).***

A mixture of II (0.01 mol; 3.76 g) and benzaldehyde (0.0l mol; 1.06 g) in absolute ethanol (50 ml) containing, sodium ethoxide (0.5 g) was refluxed for 6 hours to give III and IV.

***Formation of 6-(4-biphenyl)-2-[(2-hydrazino-carbonyl methyl) thio]-4,5-diydro-pyrimidine-4-carboxylic acid (V).***

A mixture of II (0.01 mol; 3.76 g) and hydrazine hydrate (0.01 mol; 1.14. g) in ethanol (50 ml) was refluxed for 6 hours to give V.

***Formation of 6-(4-biphenyl)-2-{[2-oxo-2(1H-triazien-1-yl)ethyl]thio}-4,5-dihydro pyrimidine-4-carboxylic acid (VI).***

A mixture of V (0.01 mol; 3.82 g) and sodium nitrite (0.01 mol; 0.68 g) in dilute HCl 10 ml. was stirring at 0 $^{o}$C temperature for 6 hours the solid that separated after washed by cold water was recrystallized from the proper solvent to give VI.

***Formation of 8-(4-biphenyl)-3-oxo-3,4-dihydro-2H, 9a H-pyrimido-[2,1-b] [1,3,4] thiodiazene-6-carboxylic acid (VII).***

A mixture of V (0.01 mol; 3.82 g) and sodium nitrite (0.01 mol; 0.68 g) containing (5 ml) conc. HCl was stirring at 10$^{o}$C temperature the resulting product was recrystallized from the proper solvent to give VII.

***Formation of 2-{[3-oxo-5-(3,4,5-trimethoxyphenyl)pyrazolidin-4-yl]thio}-6-(4-biphenyl)-4,5-dihydropyrimidine-4-carboxylic acid (VIII).***

A mixture of V (0.01 mol; 3.82 g) and 3,4,5-trimethoxy benzaldehyde (0.01 mol; 1.96 g) in ethanol (40 ml). Was refluxed for 6 hours. The solid that separated after concentration and cooling was recrystallized from the proper solvent to give VIII.

***Formation of 2-[(3,3-dimethyl-5-oxopyrazolidin-4-yl)thio]-6-(4-biphenyl)-4,5-dihydro pyrimidine-4-carboxylic acid (IX).***

A mixture of V (0.01 mol; 3.82 g) and acetone (0.01 mol; 0.58 g) in absolute ethanol (40 ml) was refluxed for 6 hours. The solid that separated after concentration and cooling was recrystallized from the proper solvent to give IX.

***Formation of 3-acetyl-6-(4-biphenyl)-2-thioxo-2,3,4,5-tetrahydro pyrimidine-4-carboxylic acid (X).***

A mixture of I (0.01 mol : 2.92 g) and acetyl chloride (5 ml) containing (10 ml) concentrated HCl was heated on a steam-bath for 2 hours. After cooling the reaction mixture was poured onto crushed ice, the product that separated was filtered, washed well with water and recrystallized from the proper solvent to give X.

***Formation of 3[5-cyano-4-(4-methoxy phenyl)-6-oxo-1,4,5,6-tetrahydro pyridine-2-yl)-2-thioxo-6-(4-biphenyl)-2,3,4,5-tetrahydropyrimidine-4-carboxylic acid (XI).***

A mixture of X (0.01 mol : 3.52 g); ethyl-2-cyano-3(4-methoxy phenyl) acrylate (0.01 mol : 2.31 g) and ammonium acetate (4 g) in absolute ethanol (50 ml) was refluxed for 6 hours. After cooling, the reaction mixture was poured onto water and the product that separated was filtered, washed well with water and recrystallized from the proper solvent to give XI.

***Formation of 3-[6-chloro-5-cyano-4-(4-methoxy phenyl)pyridine-2-yl]-2-thioxo-6-(4-biphenyl)-2,3,4,5-tetrahydro pyrimidine4-carboxylic acid (XII).***

A mixture of XI (0.01 mol : 5.36 g), phosphorus pentachloride (0.01 mol : 2.085 g) and phosphorus oxy chloride (3 ml) was refluxed on a steam bath for 1 hour. After cooling the reaction mixture was poured onto crushed ice the product that separated was filtered washed well with water and recrystallized from the proper solvent to give XII.

***Formation of 3-[8-cyano-7-(4-methoxy phenyl) tetrazolo(1,5-a) pyridin-5-yl]-2-thioxo-6-(4-biphenyl)-2,3,4,5-tetrahydropyrimid-ine-4-carboxylic acid XIII.***

A mixture of XII (0.01 mol: 5.52 g) and sodium azide (0.01 mol : 0.70 g) in acitic acid (30 ml) was refluxed for 10 hours. After concentration and cooling, the products that obtained was collected and recrystallized from the proper solvents to give XIII.

***Formation of pyrimidine derivatives XIVa-d.***

A mixture of XII (0.01 mol: 5.52 g) and primary amines (0.01 mol) in ethanol (40 ml) was refluxed for 10 hours. After concentration and cooling, the products that obtained was collected and recrystallized from the proper solvents to give XIVa-d respectively.

***Formation of pyrimidine sulfonamide derivatives XVa-c.***

A mixture of XII (0.01 mol : 5.52 g) and sulfa drugs (0.01 mol) in benzene (40 ml) was refluxed for 10 hours. After concentration and cooling, the products that obtained was collected and recrystallized from the proper solvents to give XVa-c respectively.

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**Table (1) Characterization and physical data for synthesized compounds (I-XVc).**

| Comp. No. | M.P. °C Solvent of crystallization | Yield (%) | Color of crystals | Molecular Formula (Mol. Wt.) | Analyses % | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Required | | | | | Found | | | | |
| | | | | | C | H | N | S | Cl | C | H | N | S | Cl |
| I | 220 Ethanol | 80 | Pale yellow | $C_{12}H_{14}O_2N_2S$ 292 | 69.86 | 4.79 | 9.59 | 10.96 | - | 69.9 | 4.8 | 9.6 | 11 | - |
| II | 230 Pet. Ether (60-80) | 80 | Yellow | $C_{21}H_{20}O_4N_2S$ 376 | 67.02 | 5.32 | 7.45 | 8.51 | - | 67.0 | 5.3 | 7.5 | 8.5 | - |
| III | 95 Pet. Ether (80-100) | 70 | Brown | $C_{26}H_{20}O_4N_2S$ 456 | 68.42 | 4.39 | 6.14 | 7.02 | - | 68.4; | 4.4 | 6.1 | 7.0 | - |
| IV | 80 Ethanol | 50 | Pale brown | $C_{28}H_{24}O_4N_2S$ 484 | 69.42 | 4.96 | 5.79 | 6.61 | - | 69.4 | 4.9 | 5.8 | 6.6 | - |
| V | 80 Ethanol | 75 | Brown | $C_{19}H_{18}O_3N_4S$ 382 | 59.69 | 4.71 | 14.66 | 8.38 | - | 59.7 | 4.7 | 14.7 | 8.4 | - |
| VI | 100 Ethenol | 65 | Dark yellow | $C_{19}H_{15}O_3N_5S$ 393 | 58.02 | 3.82 | 17.81 | 8.14 | - | 58.0 | 3.8 | 17.8 | 8.1 | - |
| VII | 110 Ethanol | 69 | Dark yellow | $C_{19}H_{15}O_3N_3S$ 365 | 62.30 | 3.37 | 11.48 | 8.74 | - | 62.3 | 3.4 | 11.5 | 9.1 | - |
| VIII | 234 Ethanol | 60 | Yellow | $C_{29}H_{28}O_6N_4S$ 560 | 62.14 | 5.00 | 10.00 | 5.17 | - | 62.0 | 5.1 | 9.9 | 5.0 | - |
| IX | 100 Pet. Ether (80-100) | 65 | Brown | $C_{22}H_{22}O_3N_4S$ 422 | 62.56 | 5.21 | 13.27 | 7.58 | - | 62.6 | 5.2 | 13.3 | 7.6 | - |
| X | 250 Ethanol | 85 | Yellow | $C_{19}H_{16}O_3N_2S$ 352 | 64.77 | 4.55 | 7.95 | 9.09 | - | 64.8 | 4.6 | 7.9 | 9.1 | - |

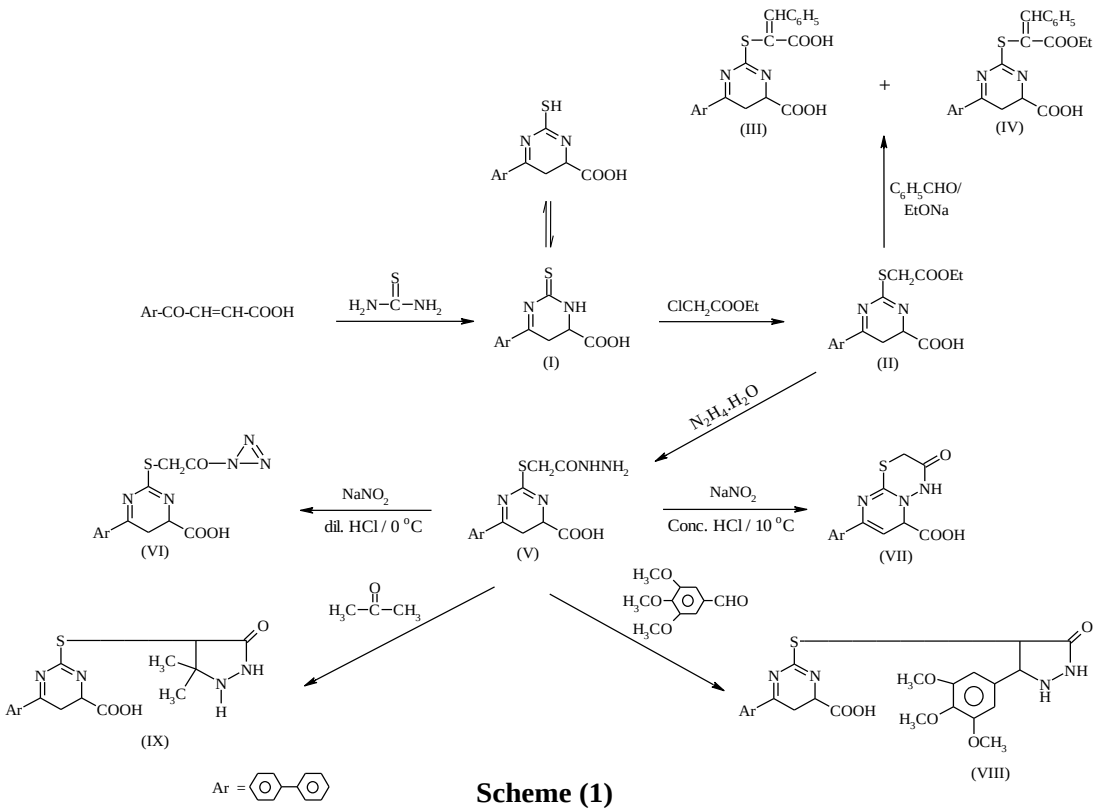
**Cont. Table (1)**

| Comp. No. | M.P. °C Solvent of crystallization | Yield (%) | Color of crystals | Molecular Formula (Mol. Wt.) | Analyses % | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Required | | | | | Found | | | | |
| | | | | | C | H | N | S | Cl | C | H | N | S | Cl |
| XI | 55 Ethanol | 83 | Brown | $C_{30}H_{24}O_4N_4S$ 536 | 67.16 | 4.47 | 10.45 | 5.97 | - | 67.2 | 4.5 | 10.5 | 6.0 | - |
| XII | 70 Chloroform | 82 | Dark brown | $C_{30}H_{21}O_3N_4SCl$ 552 | 62.16 | 3.80 | 10.14 | 5.79 | 6.43 | 62.2 | 3.8 | 10.1 | 5.8 | 6.4 |
| XIII | 100 Acetic acid | 65 | Black | $C_{30}H_{23}O_3N_7S$ 561 | 64.71 | 4.09 | 17.47 | 5.70 | - | 64.7 | 4.0 | 17.5 | 5.7 | - |
| XIVa | 74 Ethanol | 70 | Black | $C_{35}H_{27}O_3N_6S$ 611 | 68.74 | 4.42 | 13.75 | 5.24 | - | 68.7 | 4.4 | 13.8 | 5.2 | - |
| XIVb | 50 Pet. Ether (60-80) | 70 | Black | $C_{33}H_{29}O_5N_5S$ 575 | 68.87 | 5.04 | 12.17 | 5.57 | - | 68.9 | 5.0 | 12.2 | 5.6 | - |
| XIVc | 95 Ethanol | 60 | Brown | $C_{30}H_{26}O_3N_6S$ 550 | 65.45 | 4.73 | 15.27 | 5.82 | - | 65.5 | 4.7 | 15.3 | 5.8 | - |
| XIVd | 80 Ethanol | 60 | Yellow | $C_{36}H_{23}O_5N_6S$ 651 | 66.36 | 3.53 | 12.30 | 4.92 | - | 66.4 | 4.0 | 12.3 | 4.9 | - |
| XVa | 150 Benzene | 65 | Yellow | $C_{40}H_{31}O_6N_7S_2$ 769 | 62.42 | 4.03 | 12.74 | 8.32 | - | 62.3 | 4.0 | 12.7 | 8.3 | - |
| XVb | 180 Benzene | 70 | Brown | $C_{42}H_{34}O_5N_8S_2$ 794 | 63.48 | 4.28 | 14.11 | 8.06 | - | 63.5 | 4.3 | 14.1 | 8.0 | - |
| XVc | 200 Benzene Pet. Ether (60-80) | 72 | Pale brown | $C_{37}H_{30}O_5N_8S_2$ 730 | 60.82 | 4.11 | 15.34 | 8.77 | - | 60.8 | 4.1 | 15.3 | 9.0 | - |

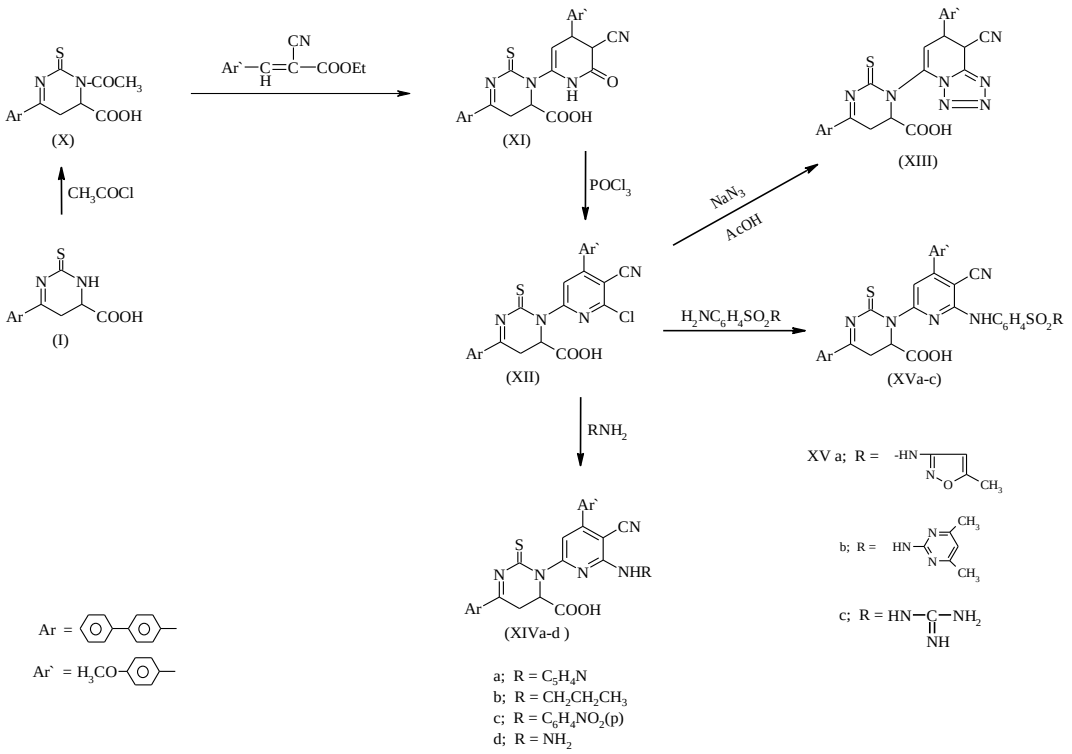
**Table (3) Antimicrobial activity of some compounds at different concentration (μg/mL) and inhibition zones (mm)**

| Compd. No. | (A) Gram-positive | | | | | | | | (B) Gram-negative | | | | | | | | (C) Antifungal activities | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Staphlococcus aurous (ATCC-6538-1`) | | | | Bacillus cereus (NRRL-B-569) | | | | Serratia marcesens (IMRU-70) | | | | Proteus merabitis (NTC-289) | | | | As pergillus fumgytus (U.G-29) | | | |
| | 75 | 125 | 175 | 250 | 75 | 125 | 175 | 250 | 75 | 125 | 175 | 250 | 75 | 125 | 175 | 250 | 75 | 125 | 175 | 250 |
| III | + | + | ++ | +++ | + | + | ++ | ++ | + | + | ++ | +++ | + | + | ++ | ++ | R | R | + | + |
| IV | ++ | ++ | +++ | +++ | + | ++ | +++ | +++ | + | ++ | ++ | +++ | + | ++ | +++ | +++ | R | R | ++ | +++ |
| V | +++ | +++ | ++++ | +++ | ++ | +++ | ++++ | ++++ | ++ | +++ | +++ | +++ | ++ | ++ | +++ | ++++ | + | ++ | ++ | +++ |
| VII | + | ++ | ++ | +++ | + | ++ | +++ | +++ | + | ++ | ++ | +++ | + | ++ | +++ | +++ | R | + | + | +++ |
| VIII | + | ++ | ++ | +++ | + | + | ++ | ++ | + | + | ++ | ++ | + | + | ++ | +++ | R | + | + | + |
| IX | ++ | ++ | ++ | +++ | + | + | ++ | +++ | ++ | ++ | ++ | ++ | + | + | ++ | +++ | + | + | ++ | ++ |
| X | + | ++ | +++ | +++ | + | ++ | ++ | +++ | + | ++ | ++ | +++ | + | ++ | +++ | +++ | + | + | +++ | +++ |
| XI | ++ | +++ | +++ | +++ | ++ | +++ | +++ | ++++ | ++ | +++ | +++ | +++ | ++ | ++ | +++ | ++++ | + | + | ++ | +++ |
| XII | ++ | ++ | ++ | +++ | ++ | +++ | +++ | ++++ | ++ | ++ | ++ | +++ | ++ | ++ | ++ | ++++ | ++ | ++ | ++ | +++ |
| XIII | + | + | ++ | +++ | + | ++ | +++ | +++ | + | + | ++ | +++ | + | + | ++ | +++ | R | + | ++ | ++ |
| XIVa | + | + | +++ | +++ | + | ++ | ++ | ++ | + | +++ | +++ | +++ | + | ++ | +++ | +++ | + | ++ | +++ | ++ |
| XVa | ++ | ++ | ++++ | +++ | ++ | +++ | +++ | ++++ | + | ++ | +++ | +++ | ++ | +++ | +++ | +++ | ++ | +++ | +++ | +++ |
| XVb | ++ | ++ | +++ | +++ | ++ | +++ | +++ | ++++ | ++ | ++ | +++ | +++ | ++ | ++ | ++ | +++ | ++ | ++ | +++ | +++ |
| XVc | ++ | ++ | ++ | +++ | + | ++ | ++ | +++ | + | ++ | ++ | +++ | + | ++ | ++ | +++ | R | + | ++ | ++ |

R : Resistance; + : Less activity (0. 2-0.5 cm); ++ : Moderate activity (0.6-1.4 cm);
+++ : High activity (1.5-2.0 cm); ++++ : Very high activity (over 3.0 cm).


Ar-CO-CH=CH-COOH
(I)
(II)
(III)
(IV)
(V)
(VI)
(VII)
(VIII)
(IX)
ClCH2COOEt
C6H5CHO/ EtONa
N2H4.H2O
NaNO2 dil. HCl / 0 °C
NaNO2 Conc. HCl / 10 °C
Ar = COOH

**Scheme (1)**


(X)
(I)
(XI)
(XII)
(XIII)
(XVa-c)
(XIVa-d )
XV a; R =
b; R =
c; R =
Ar =
Ar` = H3CO
a; R = C5H4N
b; R = CH2CH2CH3
c; R = C6H4NO2(p)
d; R = NH2

**Scheme (2)**

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**Table (2): spectral data of the new synthesized compounds.**

| Compd. No. | IR (KBr) ν Max. $Cm^{-1}$ | $^1$H-NMR (DMSO. $d_6$) δ ppm. |
|---|---|---|
| I | 3244(NH); 1700 (C=O); 1222(C=S) | δ=2.63 (t, 1H, CH), 2.8 (d, 2H, $CH_2$), 7.45-8.01 (m, 10H, Ar-H + NH), 11.02 (s, 1H, OH). |
| II | 1732(C=O) ester; 1710(C=O) acid; 1602(C=N). | δ=1.34 (t, 3H, $CH_3$ ester), 3.40 (t, 1H, CH), 3.88 (s, 2H, $CH_2$), 4.36 (q, 2H, $CH_2$ ester), 4.61 (d, 2H, $CH_2$), 7.14-8.32 (m, 9H, Ar-H), 12.59 (s, 1H, OH). |
| III | 1726(C=O); 1598(C=N). | δ=2.60 (t, 1H, CH), 3.51 (d, 2H, $CH_2$), 7.48-7.97 (m, 10H, Ar-H and C=CH-), 11.00 (s, 2H, 2 OH). |
| IV | 1759(C=O) ester; 1700(C=O)acid; 1620(C=N). | δ=0.92 (t, 3H, $CH_3$ ester), 2.31 (t, 1H, CH), 3.68 (d, 2H, $CH_2$), 4.21 (q, 2H, $CH_2$ ester), 7.11-8.10 (m, 15H, Ar-H and C=CH-), 11,11 (s, 1H, OH). |
| V | 3358, 3206(NH,$NH_2$); 1700(C=O) acid, 1668(C=O) amid; 1596(C=N). | δ=2.98 (t, 1H, CH), 3.91 (d, 2H, $CH_2$), 3.99 (s, 2H, $SCH_2$), 7.17-8.07 (m, 11H, Ar-H + $NH_2$), 11.19 (s, 1H, NH), 11.21 (s, 1H, OH). |
| VI | 3032(CH arom.); 1700(C=O) acid; 1662(C=O) amid; 1612(C=N). | δ=2.21 (d, 2H, $CH_2$), 2.79 (t, 1H, CH), 4.32 (s, 2H, $SCH_2$), 7.21-8.22 (m, 9H, Ar-H), 11.07 (s, 1H, OH). |
| VII | 1700(C=O) acid; 1659(C=O) amid; 1639(C=N). | δ=3.91 (d, 2H, 2 CH), 4.21 (s, 2H, $CH_2CO$), 7.15-8.10 (m, 10H, Ar-H + NH), 11.07 (s, 1H, OH). |
| VIII | 3200(NH); 2920(CH aliph.); 1700(C=O) acid; 1668(C=O) amid; 1614(C=N). | δ=2.61 (t, 1H, CH), 3.43 (d, 2H, $CH_2$), 3.73 (s, 9H, 3 $OCH_3$), 7.01-8.31 (m, 13H, Ar-H + 2 CH pyrazole), 9.31, 9.41 (2 s, 2H, 2NH). |
| IX | 3062(NH); 1700(C=O) acid; 1684(C=O) amid; 1598(C=N). | |
| X | 1710(C=O) acid; 1679(C=O) acetyl; 1601(C=N); 1243(C=S). | |
| XI | 3200(NH); 2214(C≡N); 1716(C=O)acid; 1678(C=O) amid; 1585(C=N); 1211(C=S). | |
| XII | 2214(C≡N); 1716(C=O) acid; 1585(C=N); 1211(C=S). | |
| XIII | 2214(C≡N); 1700(C=O) acid; 1596(C=N); 1261(C=S). | |
| XIVa | 3402, 3200(NH); 2214(C≡N); 1712(C=O) acid 1612(C=N); 1211(C=S). | |
| XIVb | 3371(NH); 2218(C≡N); 1700(C=O) acid; 1600(C=N); 1211(C=S). | δ=0.91 (t, 3H, $CH_3$), 1.59- 1.91 (m, 4H, 2 $CH_2$), 2.81 (t, 1H, CH pyrimidine), 3.91 (s, 3H, $OCH_3$), 4.31 (d, 2H, $CH_2$) 7.11-8.11 (m, 14 H, Ar-H + NH), 8.33 (s, 1H, OH). |
| XIVc | 3250(NH); 2214(C≡N); 1710(C=O) acid; 1550(C=N); 1349($NO_2$); 1211(C=S). | |
| XIVd | 3250, 3147($NH_2$); 2221(C≡N); 1700(C=O) acid; 1600(C=N); 1250(C=S). | |
| XVa | 3298, 3214(NH); 2214(C≡N); 1710(C=O) acid; 1598(C=N); 1265(C=S). | |
| XVb | 3345, 3238(NH); 2220(C≡N); 1710(C=O) acid; 1597(C=N); 1263(C=S). | |
| XVc | 3339, 3208(NH, $NH_2$); 2219(C≡N); 1710(C=O) acid; 1599(C=N); 1236(C=S). | δ=1.21 (t, 1H, CH), 2.22 (d, 2H, $CH_2$), 3.61 (s, 4H, $OCH_3$ + CH pyridine), 5.22 (s, 2H, $NH_2$), 7.06-7.35 (m, 2 OH, Ar-H + 3 NH), 8.11 (s, 1H, OH). |

**References**

1. P.G. BARALDE; M.G. PAVANE; M. NUNEZ; P. BRIGIDI, B. VITALI; R. GAMBARI AND R. ROMAGNOLI. , Bioorg. Med. Chem. 10(2002) 449-456.
2. A. KUMAR, S. SINHA AND M.S. CHAUKAN., Bioorg. Med. Chem. Lett 12(2002) 667-670.
3. M.N. NASR AND M.M. GINEINAH., Arch. Pharm. 335(2002) 289-295.
4. S.M. SONDHI; M. JOHAR; S. RAJVANSHI; S.G. DOSTIDAR; R. SHUKLA; R. RAGHUBIR AND J.W. Lown., Aust. J. Chem. 54(2001) 69-74.
5. S.M. SONDHI. R.N. GOYAL, A.M. LAHOTI, N. SINGH, R. SHUKLA AND R. RAGHUBIR. Bioorg and Med. Chem. 13(2005) 3185-3195.
6. A. GANGJEE, A. VIDRVANS, E. ELZEIN, J.J. MC GUIRE, S.F. QUEENER AND R.L. KISLIUK. J. Med. Chem. 44(2001) 1993-2003.
7. N. KUMAR; G. SINGH AND A.K. YADOV. Heteroat. Chem. 12(2001) 52-56.
8. G. MANGALAGIU, M. UNGUREANU, G. GROSW, I. MANGOLAGIU AND M. PETROVANU. Ann. Pharm. Fr 59(2001) 139-140.
9. J. GRIFFON; J.A. MONTGOMERY AND J.A. SECRIST. Nucleosides Nucleotides 20(2001) 649-652.
10. C.J. SHISHOO; U.S. SHIRSATH; I.S. RATHOD, M.J. PATIL AND S.S. BHARGAVA., Arzneim Forsh. 51(2001) 221-231.
11. O. BRUNO, G. BRULLO, S. SCHENONE; A. RANISE; F. BONDAVALLI, E. BOROCELLI, M. TOGNOLINI; F. MAGNAMINI AND V. BOLLABENE. Farmeco. 57(2002) 753-758.
12. G. MUSTAZZA, M.R.D. GAIDICE, A. BORIONI AND F. GATTA. J. Heterocycl. Chem 38(2001) 1119-1130.