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RESEARCH ARTICLE

Synthesis of some new thiazolo, pyrano and pyrimidinone derivatives of expected biological activities

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Abstract

Reaction of 6-hydroxy-2-thio-2,3-dihydro 1-H-pyrimidin-4-one(1) with phenacylbromide, monochloro acetic acid, ketones, 1,2-dibromo ethane and 1,3-dichloropropane to yield thiazolo [3,2-a] pyrimidin-5-one derivatives (2-7a,b).

Condensation of **(1)** with chalcones and hydrazonoyl chloride gave compounds **(8a,b), (9a,b)** and **(10a,b)** respectively. On the other hand condensation of **8a** with chlorocetic acid gave compound **(11)**, which react with benzaldehyde to give **12**, the allowed compound **12** react with $NH_2OH.HCl$ to give compound **13**. Condensation of **(8a)** with ketones, phenacyl bromide, 1,2-dibromoethane, 1,3-dichloropropane and hydrazonoyl chloride to gave pyrano pyrimidinone derivatives **(14-19),** also compound **(8a)** reacted with acetic acid with added drops of conc. H_2SO_4 gives bis compound **(20).**

INTRODUCTION

Since resistance to antimicrobial drugs is wide spread, there is an increasing need for identification of novel structure lead that may be used in designing new potent and less toxic antimicrobial agents. Many thiazolopyrimidinone derivatives are reported to exhibit antimicrobial[1-6], antiviral[7-10] antihypertensive[11], antihistaminic[12], neurotropic[13], anticonvulsant[14] antidepressant, sedative, analgesic[15-19] and anti-cancer activities. Pyrano pyrimidinone derivatives including physiological and biological properties[20].

Results and Discussion:

The new derivatives were prepared according to the reaction sequences depicted in schemes 1,2. Reaction of equimolar amounts of 6-hydroxy-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one(1)[21] with phenocyl bromide in boiling ethanol and in presence of catalytic amount of sodium hydroxide solution afforded 7-hydroxy-3-phenyl thiazolo[3,2-a]pyrimidine-5-one(2), through rearrangement of compound **1** to the thiol form followed by elimination of one molecule of each of HBr and H_2O. Similarly reaction of 1 with chloroacetic acid in presence of anhydrous sodium acetate gave the thiozolopyrimidine dione (3).

On the other hand, reaction of 1 with ethyl acetoacetate, acetylatone and acetone in acetic acid and in the presence of few drops of conc. H_2SO_4, gave the corresponding thiazolo pyrimidine derivatives 4-6, respectively.

Reaction of **1** with 1,2-dibromoethane and/or 1,3-dichloro propane gave the corresponding pyrimido thiazine **7a** and pyrimido thiazein **7b**, respectively, through the thiol form of compound **1** followed by dehydroholagenation.

Reaction of **1** with 3-(4-chlorophenyl) and/or 3-(4-nitrophenyl)-1-phenyl propenone in boiling glacial acetic acid and in the presence of phosphorus pentoxide afforded the corresponding pyrano pyrimidinone **8a** and **8b**, respectively.

However, reaction of **1** with 1-methyl-3,5-bis-thiphen-2-yl methylene piperidin-4-one and 3,5-bis (4-chlorbenzylidene)-1-methyl-piperidin-4-one under the same conditions gave the corresponding triazo anthracene derivatives **9a** and **9b**, respectively.

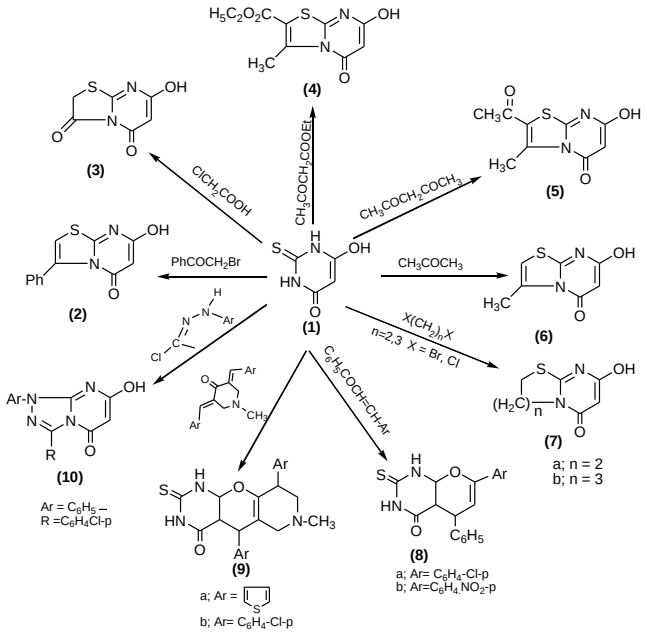
Interestingly, reaction of **1** with hydrozonoyl chloride derivative[22] gave the triazolo pyrimidinone derivative (10).

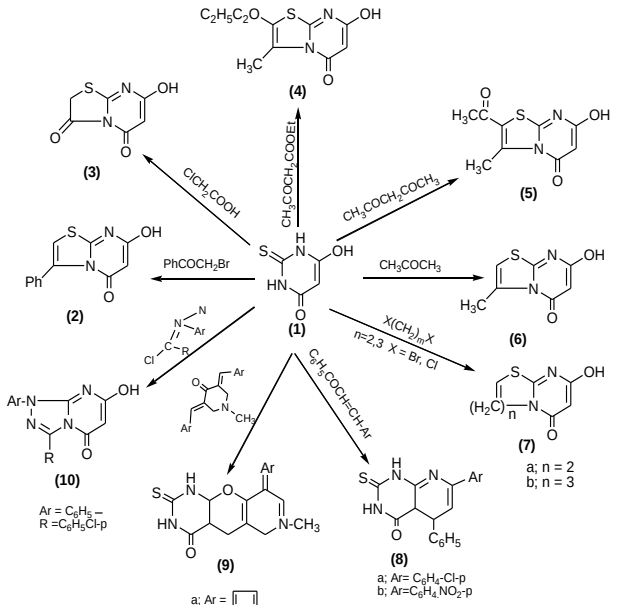
Compound **8a**, can be used as good starting material for the preparation of several condensed heterocyclic compounds. Thus, reaction of **8a** with chloroacetic acid in the presence of anhydrous sodium acetate afforded the triacyclic compound **11**, which undergo condensation with benzaldehyde to give compound **12** the latter undero cyclocondensation reaction with hydroxylamine hydrochloride as α,β-unsaturated ketone to give the corresponding tetracyclic compound **13**.

Reaction of **8a** with acetyl acetone in boiling acetic acid containing few drops of conc. H_2SO_4 gave compound **14**. However, reaction of **8a** with N-methyl pipridone, p-choroacetophenone p-nitroacetophenone and/or phenocylbromide give the corresponding triacylic compounds 15-17.

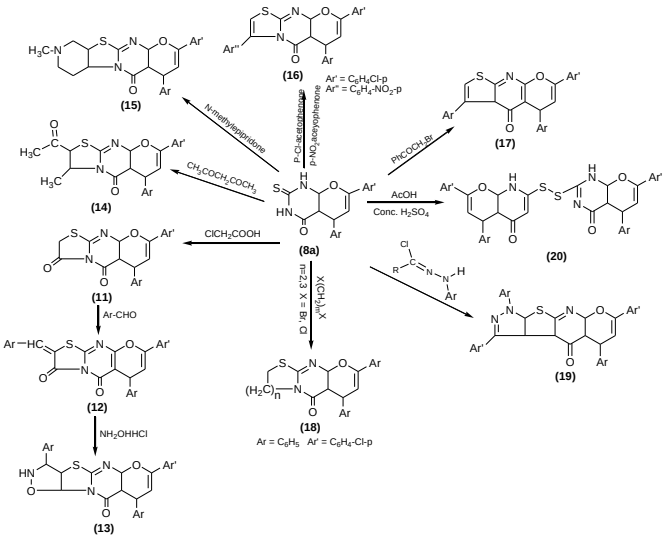
Reaction of **8a** with 1,2-dibromethane and/or 1,3-dichloropropane, afforded compound **18a** and **18b,** respectively, by a similar mechanism stated previously.

On the other, reaction of **8a** with hydrozonoyl chloride in presence of TEA and/or acetic in presence of few drops of conc. H_2SO_4 gave compound **19** and the disulfonyl derivatives **20**, respectively.





Scheme (1)



Scheme (2)

Experimental

Melting points were determined in open capillary tubes on an electrothermal 9100 digital melting point apparatus (Büchi, Sritzerland) Elmer 2400 analyzer (USA). IR spectra were recorded on a Perkin – Elmer 160 FTIR (VSA) as KBr.

The ^{1}H-and ^{13}C NMR spectra were measured on Bruker Avance digital spectropholomeler (300 and 125 MHz) instrument with chemical shift (δ) expressed in ppm downfield from TRS as internal standard in DMSO-d_6. Mass spectra were recorded on SECTOR-FILDMS and GC-MS (single phase) 200V (50-60 Hz) 30A (Germany). The

elemental analysis were carried out at the microanalitical, Faculty of Science, Cairo University by using Perkin-Elmer 2400 CHN elemental analyser.

Synthesis of 6-hydroxy-2-thio-2,3-dihydro 1H-pyrimidin-3-one(1)

A mixture of barbaturic acid (0.01 mol) and P_2S_5 (0.02 mol) in anhydrous dioxan (100ml) was refluxed for 2h at 115-120°C. When the reaction was completed zinc dust (2g) and activated chercool (1g) were added and heating was continued for 15 minutes the hot solution was filtered off, concentrated to half its volume, then poured onto ice cold water. The separated solid was filtered off and recrystallized from ethanol, yield 75% MP 300°C (reported m.p. 300°C)[23]

Synthesis of 7-hydroxy-3-phenyl-(thiazolo[3,2-a] pyrimidin-5-one(2)

A mixture of compound 1 (0.01 mol), phenacyl bromide (0.01 mol) in ethanol (20 mL) in presence of 3 mL; 10% NaOH solution was refluxed for 2h and left overnight. The formed precipitate was filtered off and recrystallized from benzene. Yield; 60% M.P. 180°C FT-IR [KBr, υ,cm^{-1}) 1647) (C=O), 3371(OH), 1601 (–C=N). ^{1}H NMR (DMSO-d_6) 7.03-7.30 (m, 5H, ArH), 6.6 (s, 1H, pyrimidinohydrogen), 6.45 (s, 1H, thiazole hydrogen), 13 (s, 1H, OH).
Anal. Calcd for $C_{12}H_8N_2O_2S$: C, 59; H, 3.30; N, 11.97. Found: C, 59; H, 3.1; N, 11.22%.

Synthesis of 7-hydroxy-thiazolo [3,2-a] pyrimidin-3,5-dione (3).

A mixture of compound **1** (0.01 0.01 mol), chloroacetic acid (0.01 mol) in acetic acid (20 mL) and anhydrous sodium acetate (0.01 mol) was gently headed on a water bath at 60°C for 2h. the mixture was cooled and poured onto cold water, the separated solid was filtered off, dried and recrystallized from benzene. Yield; 55%. M.P. 280°C FT-IR [KBr,υ,
cm^{-1}) 3360(OH), 1680 and 1650 (C=O), 1618 (–C=N). ^{1}H NMR (DMSO–d_6) 12.5 (s, 1H, OH), 6.7 (s, 1H, pyrimidine hydrogene), 6.25 (s, 2H, thiazole hydrogen). Anal. Calcd. For $C_6H_4N_2O_3S$; C, 39.13; H, 2.19; N, 15.21. Found: C, 39.1; H, 2.18; N, 15.11%.

Synthesis of 7-hydroxy-3-methyl-5-H-thiazolo[3,2-a] pyrimidine-2-carboxylic ethyl ester(4); 2-acetyl-3,5-dimethyl-isothiazolo[2,3-a] pyrimidin-7-one(5) and 7-hydroxy-3-methyl-thiazolo[3,2-a] pyrimidin-5-one(6):

A solution of **1** (0.01 mol), ethyl acetoacetate, acetylacetone and/or acetone (0.01 mol) in acetic acid (20 mL) containing few drops of conc. H_2SO_4 was refluxed for 2h. The solid obtained after cooling and neutralization of the solution with ammonium hydroxide, was filtered off, washed with water , dried and recrystallize from benzene (compound 4) ethanol (compound 5,6).
4: yield 55%. MP: 110°C. FT-IR (KBr, υ, cm^{-1}) 3360 (OH), 1700 (C=O ester), 1660 (C=O). ^{1}H NMR (DMSO-d_6) 13.5 (s,1H, OH), 6.5 (s, 1H, pyrimidine hydrogen), 2.15 (s, 3H, CH_3), 4.5 (q, 2H, $–CH_2CH_3$), 1.34-1.6(t, 3H, CH_2CH_3). Anal. Calcd. For $C_{10}H_{10}N_2O_4S$, C, 47.24; H, 3.96; N, 11.02. Found : C, 47.33; H, 3.88; N, 11.11%.
5: Yield, 45%. M.P.: 200°C. FT-IR(KBr, υ, cm^{-1}) 335(OH), 1692(C=O), 1680(C=O), 1608(–C=N). Anal . Calcd. For $C_9H_8N_2O_3S$, C, 28.21, H, 3.60, N, 12.49. Found: C, 28.11, H, 3.61, N, 12.37%.
6: Yield, 45%. M.P.: 210°C. FT-IR(KBr,υ, cm^{-1}) 3250(OH), 1560(C=N), 1655 (C=O). Anal. Calcd. For $C_7H_6N_2O_2S$, C, 46.15; H, 3.30; N, 15.38. Found: C, 46.1, H, 3.31, N, 15.41%.

Synthesis of 8-hydroxy-3,3-dihydro-2H-pyrimido[2,1-b][1,3]thiazin-6-one (7a).

To aworm solution of **1** (0.01 mol) in methanol (25 mL) containing sodium carbonate (0.02 mol) was added 1,2-dibromoethane in methanol (24 mL) containing few drops of TEA. The solution was refluxed for 8h. The formed precipitate after cooling was filtered off and recrystallized from ethanol. Yield 45%. M.P.: 220°C FT-IR (KBr,υ,cm^{-1}) 3240(OH) , 1560(C=N), 1643(C=O). ^{1}H NMR (DMSO–d_6) 14 (s,1H,OH), 1.93 (m, H, $2CH_2$), 2.78 (t, 2H, CH_2), 8.40 (s, 1H, CH). ^{13}C NMR (DMSO–d_6)21.83- 25.53 (3, CH_2), 118.34-148.96 (7c, SP^2 carbon atoms), 156.30 (C=O) Anal. Calcd. for $C_7H_8N_2O_2S$, C, 45.64, H, 4.38; N, 15.21 Found: C, 45.13, H, 4.28; N, 15.11%.

Synthesis of 2-hydroxy-6,7.8-tetrahydro-pyrimido [2,1-b][1,3] Thiazepin-4-one(7b):

A solution of **1** (0.015 mol), 1,3-dichloropropane (0.01 mol) in acetone (10mL) was added dropwise to stirred acetone (10 mL) containing few drops of T.E.A. The mixture was refluxed for 8h. the solid formed was filtered off, washed with water, 1% NaOH and 1% HCl, respectively. The remaining solid was suspended in chloroform and stirred for half an hour then filtered was evaporate to drynes and the obtained solid was

recrystallized from dioxan. Yield. 55% M.P.: 250°C. F.T. IR(KBr, υ,cm^{-1}) 3256(OH), 1601 (C=N), 1656(C=O). Anal calcd for $C_8H_{10}N_2O_2S$, C, 48.47; H, 5.08; N, 14.13. Found: C, 48.11; H, 5.10; N, 14.2 %.

Synthesis of 7-(4-chlorophenyl) and 7-(4-nitrophenyl)-5-phenyl-2-thioxo-1,2,3,4a, 8a hexahydropyrano[2,3-d] pyrimidin-4-one (8a and b):

To a solution of 1(0.005 mol) and 3-(4-chloropheny) and/or 3-(4-nitrophenyl)-1-phenyl propenone (0.005 mol) in glacial acetic acid (16 mL) was added phosphorus pentoxide (4g) and the solution was refluxed for 20 minutes with continuous stirring. The solid obtained after cooling and pouring onto crushed ice was filtered off, dried and recrystallized from ethanol to give **8a** and **8b** respectively **8a**, yield: 95% M.P.> 300C. FT-IR (KBr, υ, cm^{-1}) 3219(NH), 1668(C=O), 1238 (C=S), 116 (C–O–C) 540 (C=C).
^{1}H NMR (DMSO-d_6) 12.08 (s, 2H, 2NH), 4.22 (d, 2H, pyrane proton), 7.04-8.05 (m, 9H, phenyl proton), ^{13}C NMR 182.14 (C=S), 137.33-111.15 (Ar–C), 51.02 (CH_2), 168.33 (C=O).
Anal. Calcd. For $C_{19}H_{15}ClN_2O_2$,S: C, 61.53; H, 4.08; N, 7.55. Found: C, 61.33; H, 4.07; N, 7.35%.
8b; Yield: 75% M.P.: 140°C FT-IR (KBr, υ, cm^{-1}) 3210 (NH), 1662 (C=O), 1230 (C=S), 118(C–O–C) 1530 (C=C).
Anal. Calcd. For $C_{19}H_{15}N_3O_4S$, C, 59.83; H, 3.39; N, 11.02 Found: C, 59.33; H, 3.66; N, 11.10%.

Synthesis of 6-methyl-10-thiophene-2yl-8-thiophene-2yl-methylene-2-thioxo-dodecohydro-9-oxo-1,3,6-triaza-anthracn-4-one (9a) and 8-(4-chlorobenzyldene)-10-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4a,5,6,7,8,9a,10-decohydro-9-oxo-1,3,6-triazanthracen-4-one(9b).

To as solution of 1 (0.005 mol) and 3-cyclopenta-1,3-dienyl methylene-1-methyl-5-thiophen-2-yl methylene piperidin-4-one and/or 3,5-bis-(4-chlorbenzylidene)-1-methyl-piperidin-4-one(0.005 mol) in glacial acetic acid (16 mL) was added phosphorus pentoxide (4g) and the solution was refluxed for 20 minutes with continuous stirring. The solid obtained after cooling and pouring onto crushed ice was filtered off, dried and recrystallized from ethanol to give **9a** and **9b**, respectively.
9a; yield: 95% M.P. 280°C. FT-IR (KBr, υ, cm^{-1}) 3219(NH), 1678 (C=O), 1110(C=S).
^{1}H NMR(DMSO-d_6) 4.22 (d,H, CH pyran), 3.76 (s, 3H, N–CH_3, CH phenyl), 7.4-8.05 (m, 9H, Ar–H), 10-11 (s, 2H, 2NH)
Anal. Cacl for $C_{22}H_{26}N_3O_2S_3$: C, 57.36; H, 5.69, N, 12.1 Found: C, 5731; H, 5.61; N, 9.22%.
9a; yield: 65%. M.P. > 300C FT-IR (KBr, υ, cm^{-1}) 1670(C=O), 1112 (C=S), 3213 (NH).
Anal. Calc. for $C_{24}H_{21}Cl_2N_3O_2S$: C, 59.26; H, 4.35; N, 8.64. Found C, 59.22; H, 4.33; N, 8.3%.

Synthesis of 7-hydroxy-3-methyl-1-phenyl-1H-[1,2,4]triazolo[4,3-a] pyrimidin-5-one(10)

To a solution of 1(0.01 mol) and hydrazonoyl chloride (0.01 mol) was stirr under reflux in dry chloroform (30 ml) was stirr under reflux in dry chloroform (20 ml) in the presence of four drops of T.E.A. for 8h. the solvent was evaporate and the solid product washed with MeOH and recrystallized from ethanol yield 65% M.P. 190°CFT-IR (KBr, υ, cm^{-1}) 1660 (C=O), 1340 (OH), 1680 (C=N). ^{1}H NMR (DMSO–d_6), 15 (s, H, OH), 6.5 (s, H, CH), 4.2 (s, 3H, CH_3), 7.2 (m, 5H, phenyl). Anal. Calc. For $C_{12}H_{10}N_4O_2$: C, 59.5, H, 4.13, N, 23.14 Found: C, 23.14, C, 59.1, H, 4.32, N, 23.1%.

Synthesis of 7-(6-chloro-hexa-1,3,5-triynyl)-5-phenyl-4a,8a,dihydro-5H-8-oxa-1-thia-3a,9-diazocyclopenta[b]naphathen-3,4-dione(11)

To a solution of **8a** (0.01 mol) and chloroacetic acid (0.01 mol) in acetic acid was added anhydrous sodium acetate (0.02 mol) and the solution was gently heated with stirring on a water bath for 2h. the solid obtained after cooling and pouring onto cold water was filtered off and recrystallized from ethanol.
Yield: 65% M.P. 280°C. FT-IR (KBr, υ, cm^{-1}) 1690 (C=O), 1650 (C=O). ^{1}H NMR (DMSO–d_6) 7.4-7.7 (m, 9H, Ar–), 8.2 (s, 1H,pyroloproton), 8.25 (d, 2H,thiazoloproton) 4.5 (d,m 2H, pyroloproton). Anal. Calcd for $C_{21}H_{15}ClN_2O_3S$: C, 61.39; N, 6.82. Found. C, 61.22, H, 3.12, N, 6.13%.

2-Benzylidene-7-[6-Chloro-hexa-1,3,4-Triynl-5-phenyl-4a, 8a-dihydro-5H-8-oxa-1-thia-3a,9-diaza-cyclopent[b] naphthalene-3,4-dione(12).

To a solution of 11(0.01 mol), benzaldehyde (0.01 mol) in acetic anhydride (30 mL) was added anhydrous sodium acetate (0.02 ml) and the solution was heated under reflux for 3h. the solid obtained and cooling and pouring onto cold water was filtered off and recrystallized from DMF.
Yield: 76%. M.P. 200°C. FT-IR (KBr, υ,cm^{-1}) 1681 (C=O), 1678 (C=O) 1659 (C=N). ^{1}H NMR (DMSO-d_6) 7.31-7.80 (m, 14H, Ar–H), 7.94 (s,1H, pyroloproton), 8.25, (d,2H, thiazoloproton), 9.96 (d, 2H, pyroloproton). Anal. Calcd for $C_{28}H_{19}ClN_2O_3S$: C, 67.40; H, 3.84; N, 5.61 Found: C, 67.41; H, 3.11; N, 5.11%.

Synthesis of 7(4-chlorophenyl)-1,5-diphenyl-1,2,3a,4a,8a,10a-hexa-hydro-5H-3,8-dioxa-10-(thia-2,3b,9-triazapentalenol[1,2-b] naphthalen-4-one (13):

A solution of **12** (0.01 mol), hydroxylamine hydrochloride (0.01 mol), anhydrous sodium acetate (0.02 mol) in glacial acetic acid (30 mL) was refluxed for 5h. the solid obtained after cooling pouring onto cold water, was filtered off and recrystallized from benzene. Yield: 76%. M.P. 250°C. FT-IR (KBr, υ,cm^{-1}) 1689 (C=O), 1620 (C=N), 3310 (NH). ^{1}H NMR (DMSO–d_6) 10.58 (s, 1H, NH), 7.30-7.50 (m, 14H, Ar–H) 6.45 (s, 1H, pyrolopronton) ^{13}C–NMR 160.63 (C=N), 140-122(Ar–C), 168.55 (C=O), 49.80 (CH) Anal. Calcd. for $C_{22}H_{18}ClN_3O_3S$: C, 60.07, H, 4.12, N, 9.55. Found: C, 61.1; H, 4.11; N, 9.45%.

Synthesis of 2-acetyl-7-(6-chloro-hexa-1,3,5-triyny)-3-methyl-5-phenyl-4a,8a-dihydro-5H-8-oxa-1-thia-3a,9-diaza-cyclopenta[b] naphathlen-4-one (14).

A solution of 8a (0.01 mol), acetylacetone (0.01 mol) in acetic acid (20ml) and few drops of conc. H_2SO_4 was refluxed for 2h. The reaction mixture was cooled and neutrolized by NH_4OH. The formed precipitate was filtered off and recrystallized from ethanol. Yield : 55%. M.P. 210°C FT-IR (KBr, υ,cm^{-1}) 1695 (C=O), 1690(C=O). ^{1}H NMR (DMSO–d_6) 8.03-8.50 (m, 9H, Ar–H, 7.9 (s, 1H,) pyrozoloproton), 7.6(d, 2H, 2CH), 3.8 (s, 3H, methylproton), 3.6(s, 3H, methylproton). Anal calcd for $C_{24}H_{19}ClN_2O_3S$. C, 63.92; H, 4.25; N, 6.21 Found: C, 63.82; H, 4.11; N, 6.11%.

Synthesis of 6(4-chlorophenyl)-2-methyl-8-phenyl-1,2,3,4,4a,5a,9a, 11a-octahydro-6-H, 9-oxa-11-thia-2,4b,10-triaza-benzo[b] fluoren-5-one (15).

A solution of **8a** (0.01 mol), N-methylpiperedone (0.01 mol) in acetic acid (20 mL) containing few drops of conc. H_2SO_4= was refluxed for 2h. the reaction mixture was cooled and neutralized with NH_4OH. The obtained precipitate was filtered off and recrystallized from ethanol.

Yield: 55%. M.P.: 120°C FT-IR (KBr, υ,cm^{-1}) 1665(C=O). ^{1}H NMR (DMSO–d_6) 7.7 (s, 1H, C=CH), 7.4-7.6 (m, 9H, Ar–H), 6.5 (s, 1H, CH), 3.9 (s, 3H, CH_3), 1.76-2.24 (d, 2H, CH–CH) Anal. Calcd for $C_{25}H_{24}ClN_3O_2S$: C, 64.44; H, 5.19; ; N, 9.02 Found: C, 64.23; H, 5.21; N, 9.12%.

Synthesis of 7-(6-chloro-hexa-1,3,5-triynyl)-3-(4-chlorophenyl), (4-nitrophenyl)-5-phenyl-4a,8a-dihydro-5H-8-oxa-1,thia,3a,9-diaza-cyclopenta[b] naphthalene-4-one (16a,b).

A solution of **8a** (0.01 mol), p-chloroacetophenone and/or p-nitroacetophenone (0.01 mol) in acetic acid containing few drops of conc. H_2SO_4 was refluxed for 2h. The reaction mixture was cooled and neutralized with NH_4OH. The obtained precipitate was filtered off and recrystallized from ethanol to give **16a** and **16b** , respectively.

16a: Yield: 96%: M.P. 210°C FT-IR (KBr, υ,cm^{-1}) 1655(C=O), 1560 (C=N) Anal.calcd for $C_{27}H_{18}Cl_2N_2O_2S$. C, 64.16; H, 3.59; N, 5.54. Found: C, 64.11, H, 3.66, N, 5.43%.

16b: Yield: 75% M.P.: 230°C FT-IR (KBr, υ,cm^{-1}) 1666(C=O), 1540 (C=N). Its. Was spectra should the following abundant peaks 515(M^+, 23%), 517(M^++2) 7.6%) Anal. Calcd. $C_{27}H_{18}ClN_3O_4S$. C, 62.85; H, 3.52; N, 8.14. Found: C, 62.55, H, 3.33, N, 8.13%.

Synthesis of 7-(4-chlorophenyl)-3,5-diphenyl-4a,8a-dihydro-5H-8-oxo-1-thio-3a,9-diazo-cyclophenta[b] naphthalen-4-onr(17).

A solution of **8a** (0.01 mol), phenacylbromide (0.01) in ethanol (25mL) containing 3mL, 10% sodium hydroxide was refluxed for 2h. and left overnight. The formed precipitate was filtered off and recrystallized from ethanol.

Yield: 60% M.P. : 210°C FT-IR(KBr, υ,cm^{-1}) 1650(C=O), 1618(C=N). ^{1}H NMR (DMSO–d_6) 8.9 (s, 1H, pyrroloproton), 7.7-8.8 (m, 14H, Ar–H) 3.9(s, 1H, thiazoloproton). Anal.Calcd for $C_{27}H_{19}N_2O_2SCl$: C, 68.86; H, 4.07; N, 5.95. Found: C, 68.66; H, 4.1; N, 5.61.

Synthesis of 7(4-chlorophenyl)-5-phenyl-3,4,8a-10a-tetrrhydro-2H,5H-8-oxa-1-thia-4a-aza-anthracen-10-one (18a).

A solution of **8a** (0.01 mol) in methanol (25 ml) containing sodium carbonate (0.02 mol) was added 1,2-dibromoethane in methanol (25 ml) containing few drops of T.E.A. the solute was refluxed for 8h. The formed precipitate after cooling was filtered of and recrystallized from ethanol yield 65%, M.P. >300°C FT-IR(KBr, υ,cm^{-1}) 1650(C=O), 1115
(–C–O–C–), 1515 (C=N), ^{1}H NMR (DMSO–d_6) 7.14-7.22 (m, 9H,
2 phenyl proton), 496 (s, H, C=CH), 3.2 (s, H, CH), 4.9 (t, 4H, $2H_2$), 2.2 (d, 2H, CH_2) Anal.calcd for $C_{22}H_{19}N_2O_2SCl$: C, 64.31, H, 4.62, N, 6.82 Found: C, 64.11, H, 4.52, N, 6.22%.

Synthesis of 2-(6-chloro-hexa-1,3,5-trinyll)-4-phenyl-4-4a,7,8,10,11a-hexahydro-6H-1-oxa-9-thia-5a,11-diaza-cyclohepta[b] naphthalene-5-one(18b).

A solution of **8a** (0.01 mol), 1,3-dichloropropane (0.015 mol) in acetone (10 ml) added dropwise to stirred acetone (10 ml) containing few drops of T.E.A. the mixture was refluxed for 8h. The solid formed was filtered off, washed with water, 1% NaOH and 1% HCl, respectively. The remaining solid was suspended in chloroformed and stirred for half an hour then filtered was evaporate of dryness and the obtained solid was recrystallized from dioxan yield: 65% M.P. 240°C FT-IR(KBr, υ,cm^{-1}) 1630(C=O), 1116(–C–O–C–), 1513(C=N), ^{1}H NMR (DMSO–d_6) 7.11-7.81 (m, 9H, 2phenylproton), 4.56(s, H, C=CH), 3.5 (s,H, CH), 4.5 (t, 4H, $2H_2$), 2.2 (d, 2H, CH_2).

Synthesis of 5-(4-chlorophenyl)-1,3,7-triphenyl-1-4a,5,8a:tetrahydro-4H-8-oxa-1,2,3a, 9-tetraazo-cyclopenta[b] naphthalene(19):

A solution of **8a** (0.0 mol), hydrazonoylchloride (0.01 mol) in dry chloroform (30 mL) containing four drops of T.E.A,was refluxed with stirring for 8h. The solvent was removed under reduced pressure and the solid obtained was washed with methanol and recrystallized from ethanol.
Yield: 96% M.P. :160°C FT-IR(KBr, υ,cm^{-1}) 1680(C=O), 1601(C=N). Its mess spectra gave the following abundant peaks at m/z (M^++1) 524 (0.11%), 274 (2.83%), 222 (0.48%), 77(72.96%) Anal.Calcd for $C_{34}H_{31}O_2N_4Cl$: C, 74.64; H, 5.71; N, 10.24 Found: C, 74.44; H, 5.65; N, 10.11%.

Synthesis of 2-[4-(6-chloro-hexa-1,3,5-triynyl)-2-phenyl-4a, 5,8,8a, tetrahydro-4H-pyrano[2,3-b]pyridine-7-yl-disulfanyl].7-(4-chlorophenyl)-5-phenyl-3,4a,5,8a-tetrahydro-4-H-pyrano[2,3-d] pyridin-4-one(20)

A solution of **8a** (0.01 mol) in acetic acid (20 mL) containing few drops of conc. H_2SO_4 was refluxed for 2h. the reaction solution was cooled and neutralized with NH_4OH. The obtained solid was filtered off and recrystallized from ethanol.
Yield: 75% M.P. :300°C FT-IR(KBr, υ,cm^{-1}) 1670(C=O), 1660(C=O). 1630 (C=N), 1330(NH), 1340, (NH). Its mess spectra gave the following abundant peaks at m/z 738(M^++1) 524 (0.11%), 493(2%), 407(33%), (53%). Anal.Calcd $C_{38},H_{26}N_4O_4S_2Cl_2$: for C, 61.8; H, 3.52; N, 7.59 Found: C, 61.77, H, 3.42, N, 7.11%.

Biological assay

Antimicrobial evaluation. Antimicrobial activity of the synthesized compounds was determined in vitro by disc diffusion method (23) against a variety of phathogenic microorganisms: Salmonella typhimurium (ATCC 14028), pseudomonas fluorescens (597) (Gram-positive bacteria), Staphylocossus aureus (ATCC25923), Bacillus subtilis(ATCC 6635) Gram-negative bacteria) and two strains of fungi, Candida albicans (ATCC 10221) and Aspergillus fumigatus (identified microscopically according to Moubasher (24). Antimicrobial activities of the tested compounds were estimated by placing presterilzied filter paper discs (6 mm in diameter) impregnated with two doses of test compound (10 and 20 μg per disc) on nutrient and Maconky agar media for bacteria and on sabouround extrose agar for fungus. Dimethyl formamide (DMF) was used as a solvent for impregnation. Inhibition zones (IZ) of the test compound 37°C for bacteria and after 5 days incubation at 28°C for Fungi. Chlorampenicol and cephalothin were used as a reference drugs for bacteria, where as, cycloheximide (Sigma – Aldrich, USA) was used as reference drug for fungi.
Cell culture. –HEPG2 (human liver carcinoma),
MCF7 (human breast cancer) and HCT-116 (human colon cancer) cell lines were obtained from the Karolinska Institute, Stockhloma, Sweden. All cells were maintained in 1640RPMI mediu, except for the MCF7 cancer cells which were maintained in DMEM medium (Lonza Biowahittkar, Belgium). All the media were supplemented with 1% antibiotic-antimycotic mixture (10,000 umL^{-1}) potassium penicillin, 10.00μgmL^{-1} streptomycin sulfae, 25μgmL^{-1} amphotericin β and 1% L-=glutamine (Biowest, USA).

MTT cytotoxicity assay- cell viability was investigated using MTT [3-(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyl tetrazolium bromide] Bio Basic canda Inc., Canada) assay (25) this reaction depends on the mitochondrial reduction of yellow MTT into purple from azan. All the preceding steps were carried out in a sterile laminar air flow cabinet Biosafety class II level (Baker, SG 403 INT, USA). All incubations were done at 37% in 5% CO_2 incubator in humidified atmosphere (Sheldon, TC 2323, USA). Cells were seeded into 96 well microliter plastic plates at a concentration of (10^4 cells perwell) and allowed to adhere for 24 hours. Medium was aspirate and fresh medium (without serum was added to the cells with various concentrations of test compounds (0.001,0.1,1,10, and 100μg

mL^{-1} in DMSO) and incubated for 48 hours. Medium was separated and 40 μL MTT salt (0.01 μgmL^{-1}) was added to each well and incubated for further 4 hours to stop the reaction and dissolve any formed formazan crystals,m 200 μL of 10% sodium dodecyl sulfate (SDS) was added to each well and incubated overnight at 37°C the amount of formazan produced was measured at 595nm with a reference wavelength of 62onm as background using microplate reader (Bio-Rad Laboratories, model 3350, USA). For untreated cell (negative control), medium was added instead of test compounds. A positive adrinamycin (dox orubicin) Mr=579.9) was used as aknown cytotoxic natural agent giving 100% inhibition. Dimethyl sulfoxide (DMSO) was the vehicle used for dissolution of the tested compound and its final concentration on cells was less than 0.02%.

IC_{50} was calculated for the samples and negative control (cells with vehicle) by the probit analysis method using a simple t-test (spss statistical analysis software package /version 11, spp. Sin C., (IL), Chicago, USA.

All the newly synthesis compounds were tested for their antimicrobial activity against a variety of pathogenic microorganism using the disk diffusion method (23) at two doses of 10 and 20 μg per disc (Table 1). None of the test compound showed antimicrobial activity at the dose of 10 μg per disc, whereas at the dose of 20 μg per disc. Their in vitro antiproliferative activity against human liver cancer HEPG2 (MCF7) and human colon cancer (HCT-116) cell lines at different concentration. Compounds 4,5,8,10,13,15 , 17, were the most active with antiprolifrative activity of 90.2, 96.1, 93.2 97.2, 96.1, 90.9, and 98.5 against HEPG2, MCF7 and HCT-116 cancer cell line, respectively, where as compound 4,5,13,15,18 showed activity of 95.1, 90.1, 93.2, 92.1, 96.7 against the MCF7 cancer cell line also compound 15,18 show activity of 94.7, 94.1 Table II. Compounds that showed antiproliferative activity used to calculate their IC_5 value, which corresponds to the concentration required for 50% inhibition of cell viability. Doxorubicin, one of most effective anticancer agents, was used as a reference drug Table III in case of the HEPG2 cancer cell line, compound 5 was showed to be more potent with IC_{50} of 0.7μ moL^{-1} than doxorubicin with IC_{50} of 40 μ moL^{-1} for MCF7 cancer cell line, both 5,8,10,13,15,18 were found to be more potent with I_{50} of 0.7 μmol L^{-1} US 0.07 M mol mL^{-1}, whereas in case of the HCT-166 cancer line, again compound 5,18 were found to be more potent than doxorubicin (IC_{50} of 0.7 M mol L^{-1}, whereas in case of the HCT-166 cancer cell ine, again compound **5,18** were found to be more potent than doxorubicin (IC_{50} of 60 M mol L^{-1}) with I_{50} of 0.7 M mol L^{-1}

Table I. Antimicrobial activity of some synthesized compound (20 Mg per disc)

Compd.	S.typhimurium	P.fluorescens	S.aurens	B.subtilis	C.albicans`	A.fumigatus
6	17	33	16	22	25	13
7	8	15	32	35	27	-
8	18	13	22	-	16	11
9a	13	15	-	16	17	-
14	25	23	36	31	-	12
16a	15	13	22	21	11	15
16b	17	22	19	-	13	16
17	18	19	--	32	11	12
19	23	31	32	16	33	-
20	-	15	18	19	23	-
Inhibition zones	3-12 mm low activity		13-21 mm moderate activity		➢ 22mm high activity	

Table II. Antiproliferative activity of the newly synthesized compounds against human carcinoma cell lines

Comp.	**Inhibition growth (%)**		
	HEPG2	**MCF7**	**HCT-116**
4	**90.21**	**95.1**	**53.2**
5	**96.1**	**90.1**	**87.1**
8	**93.2**	**89.5**	**78.6**
9	**75.6**	**84.2**	**86.7**
10	**97.2**	**66.5**	**84.2**
13	**96.1**	**93.2**	**88.5**
15	**90.4**	**92.1**	**94.7**
16	**88.5**	**89.1**	**89.58**
17	**98.5**	**58.5**	**55.2**

18	**84.2**	**96.7**	**94.1**
19	**88.5**	**12.34**	**52.8**

Table III. Antiprolerative activity against human cancer cell lines

Comp.	**IC_{50} (μ Mol mL^{-1})**		
	HEPG2	**MCF7**	**HCT-116**
4	**0.0007**	**0.0007**	**-**
5	**0.0007**	**0.0007**	**0.0007**
8	**0.0007**	**-**	**-**
10	**0.0007**	**-**	**-**
13	**0.0007**	**0.0007**	**-**
15	**-**	**-**	**-**
18	**-**	**0.0007**	**0.0007**
Doxorubicin	**0.04**	**0.07**	**0.06**

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