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Some new thioxopyrimidinones, thiazolopyrimidinone derivatives using diary epoxypropanones as precursor as potential antimicrobial agents

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ABSTRACT

3-(4-chlorophenyl)-1-(2-naphthayl)-2,3-epoxypropanone **(2)** react with thiourea and urea to give 4-(4-chlorophenyl)hexahydro-6-(2-naphthyl)-2-thioxopyrimidine-5-one **(3)** and 4-(4-chlorophenyl)hexahydro-6-(2-naphthyl)pyrimidine-2,5-dione **(4)** respectively. Reaction of **(3)** with each of bromoacetic acid and 2-bromopropionic acid produced thiazolo[3,2-*a*]pyrimidine-3,6-diones **(5)** and 2-methyl-thiazolo[3,2-*a*]pyrim- idine-3,6-dione **(6)** successively. Also some new derivatives **(7-14)** were prepared from the reaction of compounds **(3)** and **(5)** with different reagent. Compound **(3)** was glycosidated with chloroethyl methyl ether and 2-chloroethanol to afford compound **(15)** and **(16)**; newly synthesized compounds were tested for their antimicrobial evaluation. Among the assayed compounds derivatives **(14a)**, **(3)**, **(8b)**, **(8c)** and **(14b)** showed the highest effect compared with the other tested compounds but not more than the satandered.

KEYWORDS

Diaryl-epoxypropanone;
Thioxopyrimidinone;
Pyrimidinone;
Thiazolo [3,2-*a*] pyrimidinedione derivatves;
Antimicrobial activity.

INTRODUCION

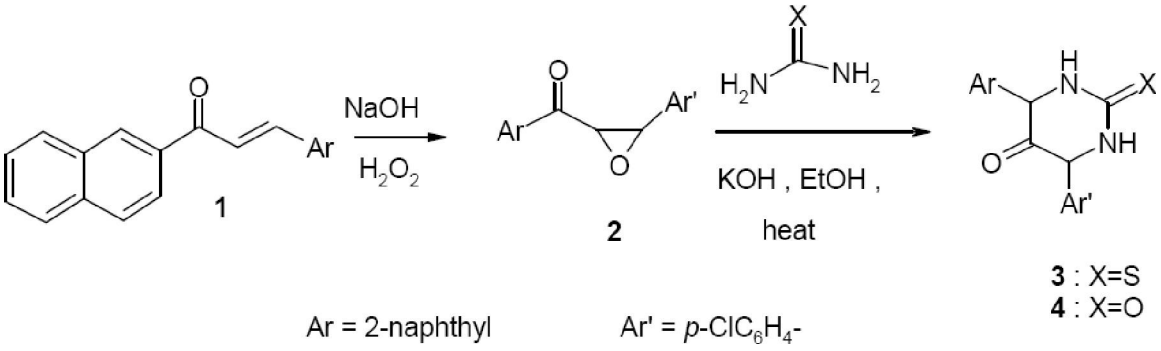
Pyrimidine derivatives have been very well known in medicinal chemistry for their therapeutic applications[1]. One possible reason for their activity is presence of a pyrimidine base in thymine, cytosine and uracil, which are essential building blocks of nucleic acids[2], Pyrimidines display a wide rang of pharmacological activites[3,4]. Various pyrimidine derivatives have been synthesized and evaluated *in vivo* and *in vitro* for their anti-inflammatory and analgesic activity[6]. Also, they revealed antibacterial[7], antiherps simplex (HSV1, HSV2)[8], analgesic[9], anticancer[10], anti-inflammatory[11], antihypertensive[12] and antifungal properties[13].

In previous work the reaction of aryl methylenecycloalkynones, pyrimidinrthiones and thiazolones was studied[14-17] and some derivatives were found to posses anticancer activity[17]. Therefore, a number of methods have been reported for the synthesis of pyrimidines derivatives[17]. Nevertheless, the development of new synthetic methods for the efficient preparation of heterocycles containing pyrimidine ring fragment is an interesting challenge. In view

of the aforementioned facts, it seemed most interesting to study the chemical behavior of 1,3-diaryl-2,3-epoxypropan-1-one **(2)** for the synthesis of some novel pyrimidine and thiazolopyrimidine derivatives with the aim to evaluate their antimicrobial activities.

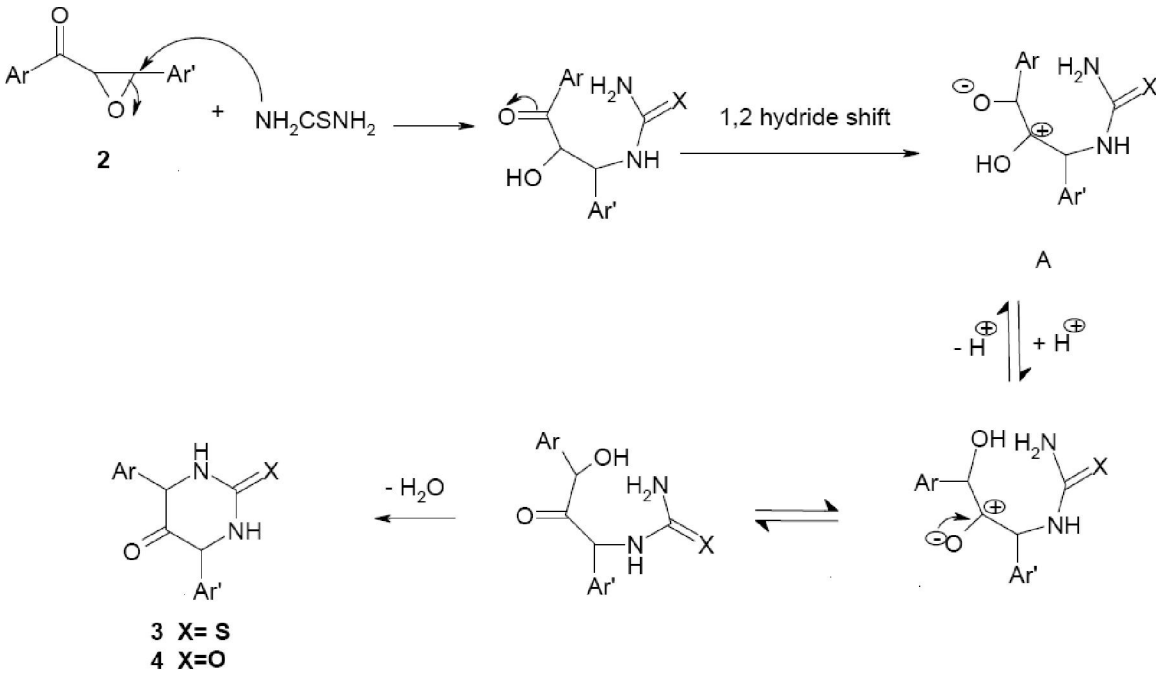
RESULT AND DISCUSSION

3-aryl-1-(2-naphthyl)propan-1-one **(1)**[18] reacts with hydrogen peroxide in alkaline medium to produce 1-(2-naphthyl)-3-(4-chlorophenyloxiranyl)methanone **(2)** which has been utilized as key starting material in the synthesis of novel many interesting heterocyclic compounds. Analytical and spectral data of compound **(2)** is in total agreement with the proposed structure (c.f. experimental section). Compound **(2)** as typical epoxide react with different nitrogen nucleophiles such as ; thiourea and urea in alcoholic potassium hydroxide solution to produce pyrimidinone derivatives **(3, 4)** respectively (c.f. experimental section) (scheme 1).



Scheme 1

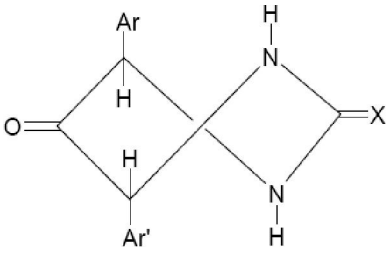
The reaction possible takes place *via* the following mechanism:



The ^{1}H NMR spectrum of compounds **(3, 4)** showed the expected signals corresponding to the aromatic protons and two types of exchangeable protons corresponding to two NH groups, besides two doublets appear corresponding to a pyrimidine protons. ^{13}C NMR spectrum of compound 3 showed signals for two SP^3 carbon, (C=O) and (C=S) (c.f. experimental).

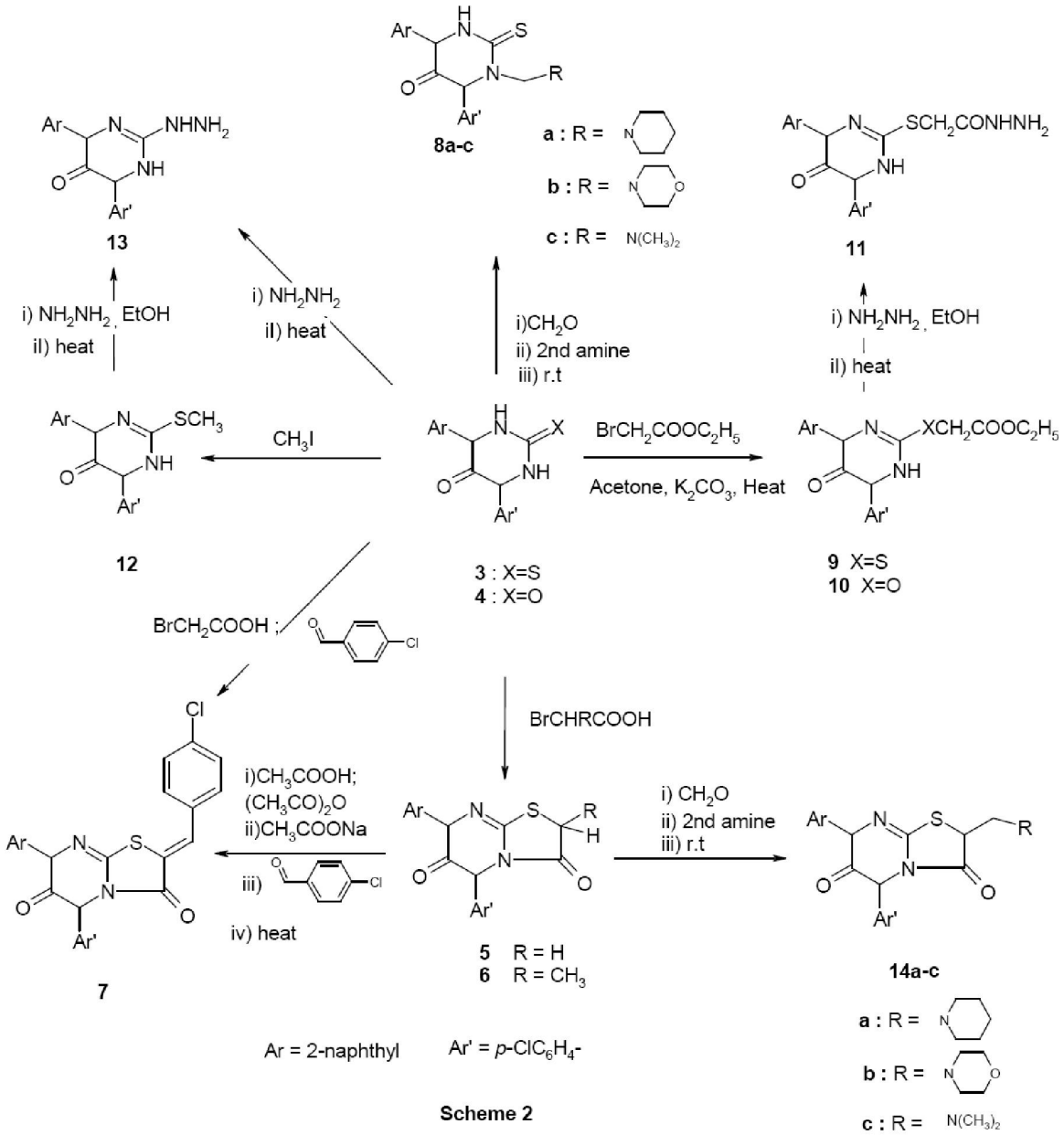
The appearance of the latter signals in ^{1}H and ^{13}C NMR spectra for compounds **(3, 4)** suggest that the produced pyrimidine ring is in fact alicyclic not aromatic[11,13]. That so many coincidences are highly improbable to be accidental, but it rather suggests that

the compound has the twist boat and not the chair[17,19] (figure 2).



Heating compound **(3)** with bromoacetic acid produced 5-(4-chlorophenyl)-7-(2-naphthyl)-2,3,5,6-tetrahydro-7*H*-thiazolo[3,2-*a*]pyrimidine-3,6-diones **(5)**[20] (scheme 2). The ^{1}H NMR spectrum of compound 5 reveled the presence of two doublets at δ 3.91; 3.97 suffer from geminal coupling for two protons at C-2 are clearly magnetically non-equivalent.

Similarly, compound **(3)** reacted with 2-bromopropionic acid to produce 2-methy-thiazolo[3,2-*a*]pyrimidine-3,6-dione **(6)**. The spectral data of compound **(6)** are compatible with the proposed structure (c.f. experimental) The presence of an active methylene group in compound **(5)** could be confirmed by with 4-chlorobenzaldehyde in to produce 2-(4-chlorobenzylidene)-5-(4-chlorophenyl)-7-(2-naphthyl)-2,3,5,6-tetrahydro-7H thiazolo[3,2-a]pyrimidine-3,6-dione 7, which directly prepared from compound **(3)** in



Scheme 2

one step by condensation with bromoacetic acid and 4-chlorobenzaldehyde to produce product identical in all aspects with compound 7 (c.f. Experimental).

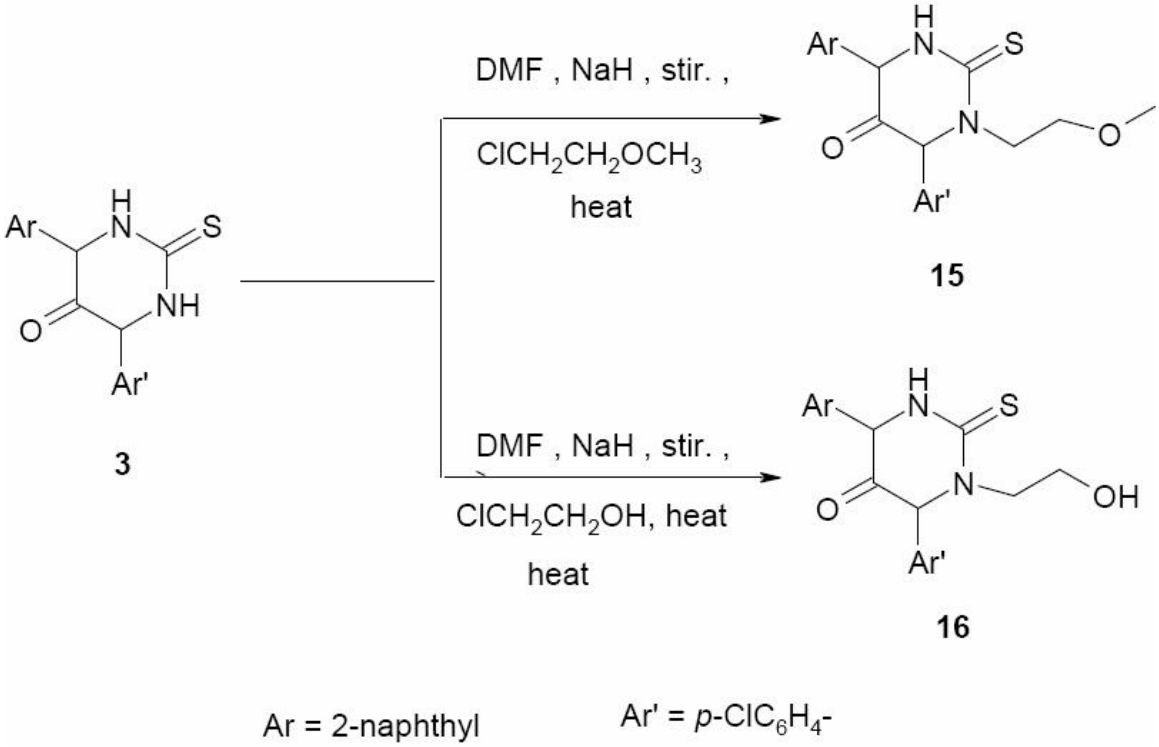
Mannich reaction on Compound **(3)**, only the 3-substituted product was isolated the 3-substituted product which proved to posses structure of compounds **(8a-c)** (scheme 2) (c.f. experimental). The presence of C=S in IR and ^{13}C NMR spectra of compound **(8a)** as an example revaled that the site of attack was on the *N*-atom and not *S*-atom[21-23] (c.f.experimental)

Compounds **(3)** and **(4)** were alkylated with ethyl bromoacetate in dry acetone, in the presence of anhydrous potassium carbonate to give 4(4-chlorophenyl)-hexahydro-6-(2-naphthyl)-pyrimidine-2-yl-thioethylacetate **(9)** and 4-(4-chlorophenyl)-hexa hydro-6-(2-naphthyl)pyrimidine-2-yl-oxoethyl acetate **(10)** successively (scheme 2). IR spectrum of compounds **(9)** and **(10)** showed absorption bands assignable to 2C=O groups and the presence of triplet, quarted and singlet signals at 1.16, 4.08 and 4.89 ppm for OCH_2CH_3 and XCH_2 protons respectively. The *O*-alkylation at C-*2* pyrimidine was confirmed by the absence of one of the C=O groups of the pyrimidine ring in compound 10 in both of IR and ^{13}C NMR spectra (scheme 2) (c.f.experimental).Compound 9 by action of hydrazine hydrate under reflux afforded the expected hydrazide **(11)** (scheme 2); identical in all aspects with compound **(11)** (c.f. experimental).

Methylation of the sodium salt of compound **(3)** with methyl iodied gave 6-(4-chlorophenyl)-2-methyl-sulfonyl-4-naphthan-2-yl-1,6-dihydropyrimidine-5-one **(12)** (scheme 2). The ^{1}H NMR spectrum showed singlet signal for CH_3, which the IR spectrum reveled absorption band for C=O group (c.f.experimental).

The hydrazine derivative **(13)** was prepared through the reaction of *S*-methyl derivatives **(12)** or thioxopyrimidine derivative 3 with hydrazine hydrate. the product revealed absorption bands for NH, NH_2 and C=O groups in the IR spectrum and its ^{1}HNMR spectrum showed signals due to NH_2 and NH (D_2O exchangeable)(c.f. experimental).

Also Mannich reaction on compound **(5)** gave 5-(4-chlorophenyl)-2-piperidin-1-ylmethyl-tetrahydro-7*H*-thiazolo[3,2-a]pyrimidine-3,6-dione **(14a)**, 5-(4-chlorophenyl)-2-morpholin-1-ylmethyl-tetrahydro-7*H*-thiazolo[3,2-a]pyrimidine-3,6-dione **(14b)** and 5-(4-chlorophenyl)-2-dimethylamino-1-ylmethyl-tetrahydro-7*H*-thiazolo[3,2-a] pyrimidine-3,6-dione **(14c)**. The ^{1}H NMR and Mass spectra of compound 14a reveled the presence of piperidine moiety (c.f. experimental section).



Scheme 3

Due to the synthesis of acyclovir as one of the most potent antiviral drugs by Schaffer *et al*[24], many attempts have been made by nucleoside chemists to prepare a number of related compounds with various side chains and glycons[25,26]. Thus, when the sodium salt of compound **(3)** (*generated in situ*) was treated with 2-chloroethyl methyl ether and 2-chloroethanol it afforded the corresponding *N*-acyclic nucleosides derivatives **(15)**, **(16)** respectively as the only isolable one product as judged by *tlc* (Scheme 3).

The structure of the aforementioned acyclic nucleosides was confirmed with spectral data and the NMR spectra which revealed methoxyethyl and hydroxyethyl signals. In addition, the IR and ^{13}C-NMR spectra revealed that the site of attack was on the N- and not S-atom. This is due to the fact that the nitrogen atom behaves as a nucleophile which attacks an electrophilic carbon of an alkyl halide[20]. The IR spectrum reveals the disappearance of one NH in compounds **(15)** and **(16)** successively as well as the existence of C=S groups (c.f.experimental).

Antimicrobial assay of prepared compounds

The antibacterial activities of the synthesized compounds were tested against *Escherichia coli* NRRL B-210 (Gram -ve bacteria), *Bacillus subtilis* NRRL B-543 and *Staphylococcus aureus* NRRL B-313 (Gram +ve bacteria) using nutrient agar medium. The antifungal activity of these compounds was also tested against *Candida albicans* NRRL Y-477 using Sabouraud dextrose agar medium. The synthesized compounds were screened in vitro for their antimicrobial activity against, by agar diffusion method[27].

RESULTS

The observed zone of inhibition is presented in TABLE 1.

The results of the preliminary screening test are listed in TABLE 1. From the data obtained in TABLE 1, it is clear that compounds 4, 11 and 14 were found to be highly active against Bacillus subtilis. But moderatly active against Escherichia coli. Compounds 7,8a, 8b, 8c, 10, 12, 15 and 17 were found to be moderately active against Bacillus subtilis; while compounds 4, 6, 7, 8a, 8b, 8c, 11, 14 and 15 were found to be slightly active against Bacillus subtilis.

TABLE 1 : In vitro antimicrobial activity by agar diffusion method of tested compounds

Tested compounds & Standards	Inhibition zone (mm)			
	Microorganism			
	Escherichia coli	Bacillus subtilis	Staphylococcus aure	Candida albeicans
Gentamycine	++++	++++	++++	-
Fluconazole	-	-	-	++++
1	-	-	-	-
2	-	-	-	-
3	+++	++	++++	-
4	+++	++++	-	-
5	-	-	-	-
6	+	+++	++	-
7	++	+++	+++	-
8a	++	+++	+++	-
8b	++	++++	+++	-
8c	++	++++	+++	-
10	++	+++	-	-
11	+++	++++	-	-
12	++	+++	-	-
13	+	++	++	-
14	+++	++++	-	+++
15	++	++++	+++	-
16	-	-	-	-
17	++	+++	-	-
18	-	-	-	-

++++ highly sensitive (inhibition zone = 25-21); +++ moderatly sensitive (inhibition zone = 20-16); ++ fairly sensitive (inhibition zone = 15-11); + slightly sensitive (inhibition zone = 10-6); -No sensitivity

EXPERIMENTAL

All melting points are uncorrected and measured using Electro-thermal IA 9100 apparatus, (Shimadzu, Tokyo, Japan). IR spectra were recorded as potassium bromide pellets on a Perkin-Elmer 1650 spectrophotometer (Perkin-Elmer, Norwalk, CT, USA). ^{1}H NMR was determined on a Jeol-Ex-300 NMR spectrometer (JEOL, Tokyo, Japan) and chemical shifts were expressed as part per million; ppm (δ values) against TMS as internal reference. Mass spectra were recorded on VG 2AM-3F mass spectrometer (Thermo electron corporation, USA) Microanalyses were operated using Mario El Mentar apparatus, Organic Microanalysis Unit, and the results were within the accepted range (±

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0.20) of the calculated values. Follow up of the reactions and checking the purity of the compounds was made by TLC on silica gel-precoted aluminum sheets (Type 60 F254, Merck, Darmstadt, Germany).

[3-(4-Chloro-phenyl)-oxirianyl]-naphthalen-2-yl-methanone (2)

Hydrogen peroxide (5mL, 30%) was added portion wise to a mixture **(1)** (0.01mole) in acetone (30mL) and methanol (15mL) containing NaOH (1g) at 0°C with stirring. The reaction mixture was left over night then cold water was added and the precipitated solid was filtered off, washed with cold water and crystallized from ethanol to give compound **(2)**.

Yield 65 %, m.p. 130-132 °C. IR spectrum. (KBr, ν, cm^{-1}): 1670 (C=O). ^{1}H NMR spectrum ($CDCl_3$, δ ppm): 4.11 (d, *J* = 14.55 Hz, 1H, epoxy-H beta to C=O), 4.39 (d, *J* = 9.55 Hz, 1H, epoxy-H alpha to C=O), 7.25-8.54 (m, 11H, Ar-H). ^{13}C NMR spectrum ($CDCl_3$, δ ppm) showed signals at: 61(C alpha to C=O), 59 (C beta to C=O), 124-130 (Ar-C), 193 (C=O); Ms m/z %: 310 (M^++2, 14), 308 (M^+, 40). *Anal*. Calcd. For $C_{19}H_{13}ClO_2$ (308.5): C, 73.90; H,4.2 ;Cl,11.50. Found: C, 73.88; H, 4.20; Cl, 11.5.

4-(4-Chloro-phenyl)-6-naphthalene-2-yl-2-thioxo-tetrahydro-pyrimidin-5-one (3)

A mixture of compounds **(2)** (0.01 mole) and thiourea (0.01 mole) in ethanolic potassium hydroxide (2 g in 100 mL ethanol) was refluxed for 4 h. The solvent was evaporated and the formed precipitate was washed several time with acidified cold water filtered off and recrystallized from prober solvent to give compound **(3)**.

Yield 75 %; m.p. 230-232°C. IR spectrum (KBr, ν, cm^{-1}): 3129-3210 (2NH), 1741 (C=O), 1435 (C=S); ^{1}H NMR spectrum ($CDCl_3$, δ ppm): 3.46 (d, *J* = 13.75 Hz, 1H, pyrimidine-H), 3.54 (d, *J* = 13.75 Hz, 1H, pyrimidine-H), 6.98-7.85 (m, 13 H, Ar-H +2NH, D_2O exchangeable); ^{13}C NMR spectrum ($CDCl_3$, δ ppm) showed signals at: 44 (CH), 73 (CH), 125-132 (Ar-C), 176(C=O), 182(C=S). Ms m/z %: 368 (M^++2, 22%), 366 (M^+, 70%). *Anal*.Calcd. for $C_{20}H_{15}ClN_2OS$ (366.86): C,65.48; H,4.09; Cl,9.68 ; N, 7.63 ; S,8.73. Found: C,65.46; H,4.08; Cl,9.69; N,7.65; S,8.71.

4-(4-Chloro-phenyl)-6-naphthalene-2-yl-tetrahydro-pyrimidine-2,5-dione (4)

A mixture of compounds 2 (0.01 mole) and urea (0.01 mole) in ethanolic potassium hydroxide (2 g in 100 mL ethanol) was refluxed for 4h. The solvent was evaporated and the formed precipitate was washed several time with acidified cold water filtered off and recrystallized from prober solvent to give compound **(4)**.

yield 77%; m.p. 218-220 °C. IR spectrum (KBr, ν, cm^{-1}): 3248, 3280 (2NH), 1721, 1766 (2C=O); ^{1}H NMR spectrum ($CDCl_3$, δ ppm): 3.41 (d, *J* = 14 Hz, 1H, pyrimidine-H), 3.56 (d, *J* = 14.5 Hz, 1H, pyrimidine-H), 6.98-7.94 (m, 15 H, Ar-H+2NH, D_2O exchangeable); ^{13}C NMR spectrum (DMSO, δ ppm) showed signals at: 68.99 (2CH), 124.35-133.08 (16Ar-C), 156.56(C=O), 175.81(C=O). Ms m/z %:352 (M^++2, 15), 350 (M^+, 50). *Anal*. Calcd. for $C_{20}H_{15}ClN_2O_2$ (350.80): C,68.47; H,4.27; Cl,10.12; N,7.98. Found: C,68.44; H,4.25; Cl,10.14; N,7.99.

5-(4-Chloro-phenyl)-7-naphthalene-2-yl-*7H*-thiazolo[3,2-a]pyrimidine-3,6-dione (5)

A mixture of compound **(3)** (0.01 mole) with bromoacetic acid (0.01mole) in acetic acid (30mL) / acetic anhydride (15mL) mixture in the presence of fused anhydrous sodium acetate (2g) was refluxed for 13h. The solution was cooled, gradually poured onto cold water and the formed precipitate was washed several times with water, filtered off and recrystallized from acetic acid to give compound **(5)**.

Yield 65 %; m.p. 240-242°C. IR spectrum (KBr, ν, cm^{-1}): 1730, 1748 (2 C=O); ^{1}H NMR spectrum ($CDCl_3$, δ ppm): 3.99(d, *J* =10 Hz, 1H, pyrimidine-H), 4.19(d, *J* =15 Hz, 1H, pyrimidine-H), 3.93(m, 2H, thiazolo-H), 7.13-7.88 (m, 11 H, Ar-H). Ms m/z %: 408 (M^++2, 2), 406(M^+, 10). *Anal*. Calcd. for $C_{22}H_{15}ClN_2O_2S$ (406.89): C,64.94 ; H,3.69; Cl,8.73; N,6.88 ; S,7.87. Found: C, 64.96; H, 3.68; Cl,8.75 ; N,6.89 ; S,7.86.

2-(4-Chloro-phenyl)-5-(4-Chloro-phenyl)-7-naphthalene-2-yl-*7H*-thiazolo[3,2-*a*]pyrimidine-3,6-dione (7)

Method A

A mixture of compound **(5)** (0.01mole) and 4-chlorobenzaldehyde (0.01mole) in acetic anhydride

(30mL) was refluxed for 11h. The solution was cooled, gradually poured onto cold water and the formed precipitate was filtered off and recrystallized from glacial acetic acid to give compound **(7)**.

Method B

A mixture of compound **(3)** (0.01mole), bromoacetic acid (0.01 mole) and 4-chlorobenzaldehyde (0.01mole) in acetic acid (30mL)/ acetic anhydride (15mL) mixture in the presence of anhydrous sodium acetate (2g) was refluxed for 15h. The solution was cooled, gradually poured onto cold water and the formed precipitate was washed several times with water, filtered off, and recrystallized from acetic acid to give compound **(7)** the product obtained her identical in all aspects with compound obtained from method A.

Yield (50 % from Method A, 60% from Method B); m.p. 251-253°C. IR spectrum (KBr, ν, cm^{-1}): 1612, 1745 (2C=O); ^{1}H NMR spectrum ($CDCl_3$, δ ppm): 3.93 (d, *J* = 13Hz, 1H, pyrimidine-H), 4.00 (d, *J* = 14 Hz, 1H, Pyrimidine-H), 7.16-7.95 (m, 16H, Ar-H+ 1H, exocyclic vinylic-H). Ms m/z %: 530 (M^++2, 25), 528 (M^+, 85). *Anal.* Calcd. for $C_{29}H_{18}Cl_2N_2O_2S$ (529.44) : C, 65.90; H, 3.40; Cl, 13.44 ; N, 5.30 ; S, 6.06. Found: C, 65.93 ; H,3.39 ; Cl, 13.43; N, 5.28; S, 6.07.

5-(4-Chloro-phenyl)-2-methyl-7-naphthalene-2-yl-*7H*-thiazolo[3,2-a]pyrimidine-3,6-dione (6)

A mixture of compound **(3)** (0.01 mole) with 2-bromopropionic acid (0.01mole) in acetic acid (30mL) / acetic anhydride (15mL) mixture in the presence of fused anhydrous sodium acetate (2g) was refluxed for 13h. The solution was cooled, gradually poured onto cold water and the formed precipitate was washed several times with water, filtered off and recrystallized from acetic acid to give compound **(6)**.

Yield 60 %; m.p. 248-250°C. IR spectrum (KBr, ν, cm^{-1}): 1720-1738 (2C=O); ^{1}H NMR spectrum ($CDCl_3$, δ ppm): 4.00 (d, *J* = 14 Hz, 1H, pyrimidine-H), 4.20 (d, *J* = 13Hz, 1H, pyrimidine-H), 2.73 (S, 3H, CH_3), 8.38 (S, 1H, OH, D_2O exchangabl), 7.27-7.88 (m, 11H, Ar-H). Ms m/z %: 422 (M^++2, 6), 420(M^+, 20). *Anal.*Calcd. for $C_{23}H_{17}ClN_2O_2S$ (420.91): C, 65.63; H, 4.04; Cl, 8.44; N, 6.65; S, 7.60. Found: C, 65.65; H, 4.03; Cl, 8.42; N, 6.66; S, 7.61.

General procedure for the synthesis of compounds (8)

Formaldehyde (1mL, 40%) was added to compound **(3)** (0.01mole) in dry ethanol (30mL) and the reaction mixture was heated for 5 minutes, cooled then 2nd amine (piperidine; morpholine; dimethylamine) (0.01 mole) was added and the reaction mixture was stirred for over night at room temperature. The formed solid was filtered off, dried and recrystallized from methanol to give compound **(9a)**,**(b)**,**(c)** respectively.

6-(4-Chloro-phenyl)-4-naphthalene-2-yl-1-piperidin-1-ylmethyl-2-thioxo-tetrahydropyrimidin-5-one (8a)

From methanol; Yield 80 %; m.p.233-235°C. IR spectrum (KBr, ν, cm^{-1}): 3294 (NH),1718(C=O),1428(C=S);^{1}HNMR spectrum (DMSO-d_6, δ ppm): 1.17-1.49(m, 6H, piperidine-H), 2.30-2.52(m, 4H, piperidine-H), 3.5-3.6 (d,*J*= 50, H pyrimidine-H), 3.7-3.8 (d,*J*= 50, H pyrimidine-H), 4.59-4.64(d,1H,NCH_2N), 4.65-4.7(d,1H,NCH_2N), 7.30-8.01(m, 12H, Ar-H+ NH, D_2O exchangeable), ^{13}C NMR spectrum ($CDCl_3$, δ ppm) showed signals at: 44 (αCH,pyrimidine), 70 (βCH, pyrimidine), 51, 63, 66 (5CH_2, pipridine), 123-132 (Ar-C), 175(C=O), 184(C=S). Ms m/z %: 463 (M^++2, 7), 461 (M^+, 20). *Anal.* Calcd. for $C_{26}H_{24}ClN_3OS$ (462.01): C,67.60 ; H,5.20 ; Cl, 7.96 ; N, 9.10 ; S, 6.93. Found: C, 67.61; H, 5.21; Cl, 7.67; N, 9.09; S, 6.95.

6-(4-Chloro-phenyl)-1-morpholin-4-ylmethyl-4-naphthalene-2-yl-2-thioxo-tetrahydropyrimidin-5-one (8b)

From methanol; Yield 80 %; m.p.238-240°C.IR spectrum (KBr, ν, cm^{-1}): 3248 (NH), 1719 (C=O), 1428 (C=S);^{1}H NMR spectrum (DMSO-d_6, δ ppm): 3.43-3.58 (m, 4H, NCH_2), 3.72-4.03(m, 4H, CH_2O), 4.61-4.64(d, *J*=15Hz,1H, pyrimidine-H), 4.66-4.96(d,*J*=15Hz,1H, pyrimidine-H), 5.30 (S, 2H, NCH_2N), 7.25-7.87 (m, 12H, 11Ar-H + NH, D_2O exchangeable). Ms m/z %: 467 (M^++2, 9), 465 (M^+, 25). *Anal.* Calcd. for $C_{25}H_{24}ClN_3O_2S$ (466.00): C, 64.44; H, 5.15; Cl,7.62; N, 9.02; S, 6.87. Found: C, 64.42; H, 5.17 ; Cl, 7.61 ; N, 9.05 ; S, 6.85.

6-(4-Chloro-phenyl)-1-dimethylaminomethyl-4-ylmethyl-4-naphthalene-2-yl-2-thioxo-tetrahydropyrimidin-5-one (8c)

From methanol;Yield 80%; m.p.243-245°C.

IRspectrum (KBr, ν, cm^{-1}): 3241 (NH), 1715 (C=O), 1419 (C=S); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 2.46(s,3H,CH_3), 1.95(s,3H,CH_3),4.26(d,*J*= 15 Hz, 1H, pyrimidine-H),4.38(d, *J* = 15 Hz, 1H, pyrimidine-H), 3.44 (dd, 2H, NCH_2N), 7.25-7.55 (m, 12H, Ar-H + 1H, NH, D_2O exchangeable). Ms m/z *%*: 425 (M^++2, 11), 423 (M^+, 35). *Anal.* Calcd. For $C_{23}H_{22}ClN_3OS$ (423.96): C, 65.17 ; H, 5.19; Cl,8.38; N, 9.91; S, 7.55. Found: C, 65.19; H, 5.18; Cl, 8.35; N, 9.90; S, 7.54.

[6-(4-Chloro-phenyl)-4-naphthalen-2-yl-5-oxo-1,4,5,6-tetrahydro-pyrimidin-2-ylsulfanyl]-acetic acid ethyl ester (9)

A mixture of compound **(3)** (0.01 mole), ethyl bromoacetate (0.01 mole), anhydrous potassium carbonate (0.04 mole) in dry acetone (30 mL) was refluxed for 24 h, on a water bath. The solvent was removed under reduce pressure then water was added to the mixture and the formed solid was filtered off, recrystallized from appropriate solvent to afford the corresponding compound **(9)**.

Yield 70%; m.p.158-160°C. IR spectrum (KBr, ν, cm^{-1}): 3222(NH), 1715, 1760 (2C=O); ^{1}H NMR spectrum ($CDCl_3$, δ ppm): 3.6 (d, *J* = 14 Hz, 1H, pyrimidine-H), 3.8 (d, *J* = 14.5 Hz, 1H, pyrimidine-H), 1.30 (t, 3H, CH_3), 4.25 (q, 2H, $COOCH_2$), 5.10 (s, 2H, OCH_2COO), 7.21-8.40 (m, 12H Ar-H +NH, D_2O exchangeable); Ms m/z %: 454 (M^++2, 6), 452 (M^+, 20). *Anal.* Calcd. for $C_{24}H_{21}Cl\,N_2SO_3$(452.96): C,63.64; H,4.64; Cl,7.84; N,6.18; S,7.67. Found: C,63.67; H,4.60; Cl,7.80; N,6.20; S,7.60.

[6-(4-Chloro-phenyl)-6-methyl-4-naphthalene-2-yl-5-oxo-tetrahydropyrimidin-2-yloxy]acetic acid ethyl ester (10)

A mixture of compound **(4)** (0.01 mole), ethyl bromoacetate (0.01 mole), anhydrous potassium carbonate (0.04 mole) in dry acetone (30 mL) was refluxed for 24 h, on a water bath. The solvent was removed under reduce pressure then water was added to the mixture and the formed solid was filtered off, recrystallized from appropriate solvent to afford the corresponding compound **(10)**.

Yield 80%;m.p.170-172°C. IR spectrum (KBr, ν, cm^{-1}): 3230(NH), 1713,1756 (2C=O); ^{1}H NMR spectrum ($CDCl_3$, δ ppm): 3.6 (d, *J* = 14 Hz, 1H, pyrimidine-H), 3.8 (d, *J* = 14.5 Hz, 1H, pyrimidine-H), 1.27 (t, 3H, CH_3), 4.21 (q, 2H, $COOCH_2$), 4.83 (s, 2H, OCH_2COO), 7.17-8.04 (m, 12H Ar-H +NH, D_2O exchangeable); Ms m/z %: 438 (M^++2, 3), 436 (M^+, 10). *Anal.* Calcd. for $C_{24}H_{21}Cl\,N_2O_4$(436.89): C, 65.97; H,4.81 ; Cl,8.13 ; N,6.41. Found: C, 65.99; H,4.78; Cl,8.14; N,6.43.

[6-(4-Chloro-phenyl)-4-naphthalene-2-yl-5-oxo-tetrahydropyrimidin-2-ylsulfanyl]acetic acid hydrazide (11)

A solution of compound **(9)** (0.01 mole) in ethanol (20 ml) and hydrazine hydrate (0.01 mole) was refluxed for 5 h. The separated solid after cooling was recrystallized from dioxan to afford the corresponding hydrazide **(11)**.

Yield 60%; mp 240-242°C; IR (KBr) (ν, cm^{-1}): 3250, 3182 (NH_2, NH), and 1655 (C=O); ^{1}H NMR (DMSO-d_6): δ (ppm) 3.32 (s, 2H, NH_2, D_2O exchangeable), 3.85 (d, *J* = 20Hz, 1H, pyrimidine-H), 4.00 (d, *J* = 20 Hz, 1H, pyrimidine-H) 3.53 (d, 2H, SCH_2), 7.03-7.95 (m, 12H Ar-H+1H,NH, D_2O exchangeable); Ms m/z (%): 440 (M^++2, 19), 438 (M^+, 60). *Anal.* Calcd. for $C_{22}H_{19}Cl\,N_4SO_2$(438.93): C,60.20; H,4.33; Cl,8.09; N,12.77; S,7.29. Found: C,60.22; H,4.30; Cl,8.04;N,12.79 S,7.27.

6-(4-Chloro-phenyl)-2-methylsulfanyl-4-naphthalene-2-yl-1,6-dihydro-4H-pyrimidin-5-one (12)

A mixture of compound **(3)** (0.01 mole) and methyl iodide (0.01mole) in ethanolic sodium ethoxide (prepared by dissolving 2g in 100 ml ethanol). the reaction mixture was refluxed for 5 hr. The solution was cooled, gradually poured onto cold water and the formed precipitate was washed several times with water to give compound **(12)**.

Yield 60 %; m.p. 200-202°C. IR spectrum (KBr, ν, cm^{-1}): 1714 (C=O), ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 2.8(S, 3H,CH_3), 3.95(d, *J* = 15 Hz, 1H, pyrimidine-H), 3.51(d, *J* = 15 Hz, 1H, pyrimidine-H), 6.94-7.91 (m, 12 H, Ar-H+NH, D_2O exchangeable). Ms m/z *%*: 382 (M^++2, 7), 380 (M^+, 20). *Anal.* Calcd. for $C_{21}H_{17}ClN_2OS$ (380.89): C, 66.22 ; H, 4.46; Cl,9.32; N, 7.35; S, 8.40. Found: C, 66.20; H, 4.47; Cl, 9.30; N, 7.37; S, 8.41.

6-(4-Chloro-phenyl)-2-hydrazino-4-naphthalene-2-yl-1,6-dihydropyrimidin-5-one (13)

Method A

A mixture of compound **(3)** (0.01mole) and excess

of hydrazine hydrate was refluxed for 3hr. The resulting solid was filtered off, washed several times with water to give compound **(13)**.

Method B

A mixture of compound **(12)** (0.01 mole) and hydrazine hydrate (0.011mole) in ethanol was refluxed for 5h. the resulting solid was collected by filtration and recrystallized from ethanol to give compound **(13)**.

Yield (70 % from method A, 60% from method B), m.p. 238-240°C. IR spectrum (KBr, ν, cm^{-1}): 3415(brNH_2), 3210 (br 2NH), 1656 (C=O); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 3.33 (d, *J* = 14 Hz, 1H, pyrimidine-H), 3.40 (d, *J* = 14 Hz, 1H, pyrimidine-H), 4.34(s, 2H, NH_2, D_2O exchangeable), 4.62(s, 1H, NH, D_2O exchangeable), 7.20-7.88 (m, 11H, Ar-H), 8.07(s, 1H, NH, D_2O exchangeable); Ms m/z *%*: 366 (M^++2, 3), 364 (M^+,10). *Anal. Calcd*. for $C_{20}H_{17}N_4OCl$ (364.83): C,66.02; H, 4.67; Cl,9.76; N, 15.40;Cl, 9.76. Found: C, 65.98; H, 4.70; Cl, 9.80 ; N, 15.37.

General method for synthesis compounds (14)

The same procedure as in preparation of compound **(9)** was performed, but compound **(5)** (0.01mole) was used to give product **(14a-c)**.

5-(4-Chloro-phenyl)-7-naphthalen-2-yl-2-piperidin-1-ylmethyl-7H-thiazolo[3,2-a]pyrimidine-3,6-dione (14a)

From dioxan; Yield 75 %; m.p. 228-230°C. IR spectrum (KBr, *v*, cm^{-1}) 1710, 1765 (2C=O), ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 1.09-1.24 (m, 6H, piperidine-H), 2.01 (m, 4H, piperidine-H), 3.07 (d, *J*=15Hz, 1H, pyrimidine-H), 3.42 (d, *J*=15Hz, 1H, pyrimidine-H), 4.53-4.61 (m, 1H, NCH_2N), 4.49-4.54 (m, 1H, NCH_2N), 5.03-5.12 (m, 1H, thiazole-H), 7.33-8.28 (m, 11H, Ar-H), Ms m/z *%*: 505 (M^++2, 0.14%), 503 (M^+, 5). *Anal.* Calcd. for $C_{28}H_{26}ClN_3O_2S$ (****): C,66.73 ; H,5.19 ; Cl, 7.05 ; N, 8.34 ; S, 6.35. Found: C, 66.72 ; H, 5.17; Cl, 7.03 ; N, 8.35; S, 6.36.

5-(4-Chloro-phenyl)-2-morpholin-4-ylmethyl-7-naphthalen-2-yl-7H-thiazolo[3,2-a]pyrimidine-3,6-dione (14b)

From dioxan; Yield 73 %; m.p. 238-240°C. IR spectrum (KBr, ν, cm^{-1}): 1690,1760 (2C=O),;^{1}H NMR spectrum ($CDCl_3$, δ ppm): 2.66-2.78 (m, 4H, 2'-H, 6'-H), 3.07 (d, *J*=15Hz, 1H, pyrimidine-H), 3.42 (d, *J*=15Hz, 1H, pyrimidine-H), 3.57-3.71 (m, 4H, 3'-H, 5'-H), 4.64 -4.71 (m, 1H, NCH_2N), 4.96-5.05 (m, 1H, NCH_2N), 5.14-5.25 (m, 1H, thiazole-H), 7.27-8.06. Ms m/z %: 507 (M^++2, 14), 505 (M^+, 45). *Anal.* Calcd. for $C_{27}H_{24}ClN_3O_3S$ (506.02): C, 64.09; H, 4.74; Cl,7.02; N, 8.30; S, 6.33. Found: C, 64.08; H, 4.75; Cl, 7.01; N, 8.33; S, 6.31.

5-(4-Chloro-phenyl)-2-dimethylaminomethyl-7-naphthalen-2-yl-7H-thiazolo[3,2-a]pyrimidine-3,6-dione (14c)

From dioxan; Yield 70 %; m.p. 243-245°C. IR spectrum (KBr, ν, cm^{-1}): 1735 (C=O), 3390(br OH); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 2.73(s,3H,CH_3), 2.74 (s, 3H, CH_3),3.38(d,*J*= 15 Hz, 1H, pyrimidine-H),3.53(d, *J* = 15 Hz, 1H, pyrimidine-H), 3.15 (S, 2H, NCH_2N), 7.17-7.92 (m, 11H, Ar-H), 9.2(s,1H, OH, D_2O exchangeable). Ms m/z *%*: 465 (M^++2, 10), 463 (M^+, 30). *Anal*. Calcd. For $C_{25}H_{22}ClN_3O_2S$ (463.98): C, 64.72 ; H, 4.74; Cl,7.65; N, 9.06; S, 6.50. Found: C, 64.70; H, 4.76; Cl, 7.67; N, 9.03; S, 6.91.

General method for synthesis (15) and (16)

A mixture of compound **(3)** (0.01mol) in DMF (5ml) containing NaH was stirred for 1h at room temperature then added (0.01mol) ethyl methyl ether; 2-chloroethanol the reaction mixture was stirred for 10h at 70°C. evaporated under reduced pressure at 70°C, the residue washed with distilled water, filtered off, dried to afford compound **(15), (16)** respectively.

6-(4-Chloro-phenyl)-1-(2-methoxy-ethyl)-4-(1,2,3,4-tetrahydro-naphthalen-2-yl)-2-thioxo-tetrahydro-pyrimidin-5-one (15)

Yield 60%; m.p. 180-182°C. IR spectrum (KBr, ν, cm^{-1}): 3280(NH), 1723(C=O), 1436(C=S); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 3.40 (d, *J* = 10Hz, 1H, pyrimidine-H), 3.44 (d, *J* =15 Hz, 1H, pyrimidine-H), 3.2(s, 3H, CH_3), 3.2(t, 2H, $CH_2CH_2OCH_3$), 3.4 (t, 2H, CH_2OCH_3), 7.19-7.84 (m, 12H, Ar-H+1H, NH exchangeable by D_2O).*Anal.* Calcd. for $C_{23}H_{21}ClSN_2O_2$(424.94): C,65.01 ; H,4.94; S,7.53; Cl,8.36; N, 6.59 Found: C, 65.00; H, 4.95; Cl, 8.34 ; N, 6.58; S, 7.55.

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6-(4-Chloro-phenyl)-1-(2-hydroxy-ethyl)-4-(1,2,3,4-tetrahydro-naphthalen-2-yl)-2-thioxo-tetrahydro-pyrimidin-5-one (16)

Yield 57 %; m.p. 188-190°C. IR spectrum (KBr, ν, cm^{-1}): 3441 (OH), 3187(NH), 1616(C=O), 1450(C=S); ^1H NMR spectrum (DMSO-d_6, δ ppm): 3.47 (d, *J* = 10 Hz, 1H, pyrimidine-H),3.41 (d, *J* = 10 Hz, 1H, pyrimidine-H), 3.84 (t, 2H, CH_2CH_2OH), 4.01 (t, 2H, CH_2OH), 7.02-7.90(m, 12H, Ar-H+1H, NH exchangeable by D_2O), 6.5(s, 1H,OH exchangeable by D_2O). *Anal.* Calcd. for $C_{24}H_{23}ClSN_2O_3$(454.97): C,63.36 ; H,5.06; S,7.04; Cl,7.81; N, 6.16 Found: C, 63.38; H, 5.05; Cl, 7.80 ; N, 6.17; S, 7.03.

Agar diffusion medium

0.5 ml suspension of each of the aforementioned microorganisms was added to sterile nutrient agar media at 45°C and the mixture was transferred to sterile Petri dishes and allowed to solidify. Holes of 0.9cm in diameter were made using a cork borer. Amounts of 0.1ml of the synthesized compounds were poured inside the holes. A hole filled with DMSO was also used as control. The plates were left for 1 hour at room temperature as a period of pre-incubation diffusion to minimize the effects to variation in time between the applications of the different solutions. The diameters of the inhibition zone of were measured and compared with that of the standard and the values were tabulated. The same method was carried out using Sabouraud dextrose agar medium on using *Candida albicans* NRRL Y-477. The plates were then incubated at 30°C for 24 hours and observed for antibacterial activity.

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