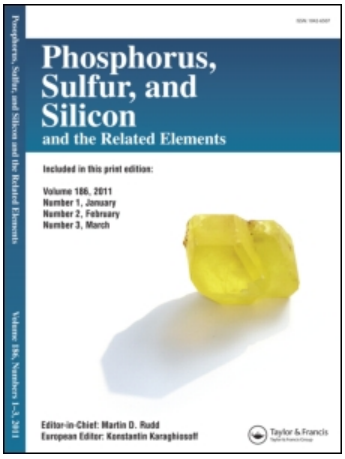

Phosphorus, Sulfur, and Silicon and the Related Elements

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A Novel Synthesis of Some New Pyrimidine and Thiazolopyrimidine Derivatives for Anticancer Evaluation

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A Novel Synthesis of Some New Pyrimidine and Thiazolopyrimidine Derivatives for Anticancer Evaluation

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*Diaryl-oxiran-2-yl methanones (**2**) were prepared and reacted with thiourea to give 2-thioxo-tetrahydro-pyrimidine-5(2H)-ones (**3**).The latter compounds reacted with bromoacetic acid to afford the title compounds (**4**). Also some new derivatives were prepared from the reaction of compounds (**3**) and (**4**) with different reagents. Compounds (**3**) were glycosidated with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosylbromide (α-ABG) to afford the corresponding nucleosides.*

Keywords 1,3-Diaryl-prop-2-en-1-ones; 1,3-diaryl-2,3-epoxypropanones; 4,6-diaryl-hexahydro-2-thioxopyrimidin-5-ones; anticancer and antimicrobial activity

INTRODUCTION

Oxiranes (epoxides) are extremely reactive organic precursors that can be used to synthesize several types of organic compounds.[1–5] In previous work, the reaction of aryl methylenecycloalkanones with thiourea to form biologically active pyrimidinethiones and thiazolones was studied.[6–8] In this article, we would like to report the use

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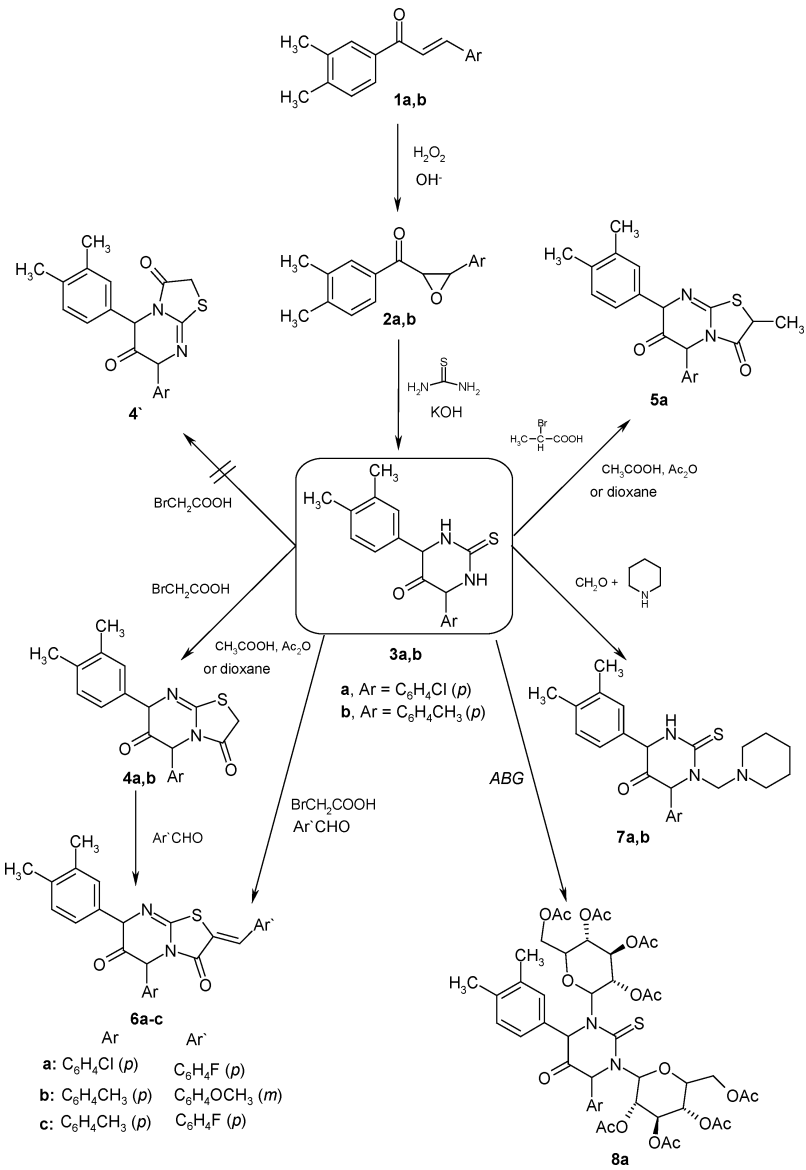
1,3-diaryl-2,3-epoxypropan-1-ones (**2**) for the synthesis of some heterocyclic compounds and their biological evaluation.

RESULTS AND DISCUSSION

3-(4-Chloro-phenyl)-1-(3,4-dimethyl-phenyl)-propenone (**1a**) and 1-(3,4-dimethyl-phenyl)-3-*p*-tolyl-propenone (**1b**)[9] reacted with hydrogen peroxide in alkaline medium to produce [3-(4-chloro-phenyl)-oxiranyl]-(3,4-dimethyl-phenyl)-methanone (**2a**) and (3,4-dimethyl-phenyl)-(3-*p*-tolyl-oxiranyl)-methanone (**2b**), respectively which have been utilized as key starting materials in the synthesis of many interesting heterocyclic compounds (Scheme 1). Analytical and spectral data of compounds (**2**) are in total agreement with the proposed structure (c.f. Experimental Section). Compounds (**2**), as a typical epoxides, reacted with thiourea in alcoholic potassium hydroxide solution to produce 4-(4-chloro-phenyl)-6-(3,4-dimethyl-phenyl)-2-thioxo-tetrahydro-pyrimidin-5-one (**3a**) and 4-(3,4-dimethyl-phenyl)-2-thioxo-6-p-tolyl-tetrahydro-pyrimidin-5-one (**3b**). The reaction possible takes place via the following (Figure 1).

Compounds (**3)** showed corrected value in elemental analysis as well as compatible IR spectral data. ^{1}H NMR spectrum (DMSO-d_6) of compound (**3b**) as an example showed the expected signals corresponding to the aromatic protons and two types of exchangeable protons corresponding to two types of NH groups, besides two doublets appear at δ 3.006 and 3.386 ppm, each corresponds to a pyrimidine protons.^{13}C NMR spectrum of compound (**3b**) showed the expected signals for C=O at 181.411, C=S at 175.891, aromatic carbons at 122.792–136.506, and two signals in the SP^3 carbon region at 42.892 and 71.480. The appearance of the latter signals in ^{13}C NMR spectrum and the two signals at δ 3.006 and 3.386 ppm in ^{1}H NMR spectrum of compound (**3b**) suggests that the produced pyrimidine ring is in fact alicyclic not aromatic and be in twist boat form, in which the oxirane nucleus undergoes hetero ring opening by thiourea at β-carbon followed by 1,2-hydride shift and proton transfer affording the fleeting intermediate (A). The latter undergoes ring closure to give the desired products (**3**). The two protons at C-4 and C-6 can undergo long rang coupling and they both appear as doublets. Compounds (**3a**) and (**3b**) are colorless (this ruled out thioquinone structure).

In the twist boat, the observed Raman spectrum of 1,4-cyclohexanedione showed seven bands, all which showed coincidences in the infrared) (Figure 2).[10] 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.



SCHEME 1

Heating compounds under reflux (**3**) with bromoacetic acid in acetic acid/acetic anhydride mixture in the presence of fused anhydrous sodium acetate produced 5-(4-chloro-phenyl)-7-(3,4-dimethyl-phenyl)-tetrahydro-7*H*-thiazolo[3,2-*a*]pyrimidine-3,6-dione

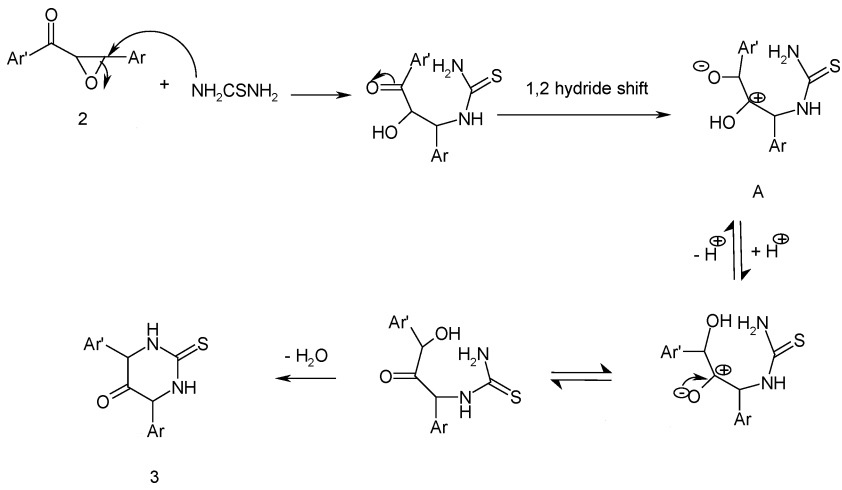


FIGURE 1 Mechanism of formation of compounds (**3**).

(**4a**) and 7-(3,4-dimethyl-phenyl)-5-*p*-tolyl-tetrahydro-7*H*-thiazolo[3,2-*a*]pyrimidine-3,6-dione (**4b**), rather than their isomer (**4′**)[11] (Scheme 1). Compounds **(4)** gave corrected value in elemental analysis besides displaying the expected carbonyl absorption bands in the IR spectra (c.f., Experimental section). The two protons at C-2 are clearly magnetically non-equivalent and they suffer from geminal coupling which led to the appearance of two doublets at δ 4.457 and 4.568 ppm.

Similarly, compounds (**3**) reacted with 2-bromopropionic acid, under the same reaction conditions to produce 5-(4-chloro-phenyl)-7-(3,4-dimethyl-phenyl)-2-methyl-tetrahydro-7*H*-thiazolo[3,2-*a*]pyrimidine-

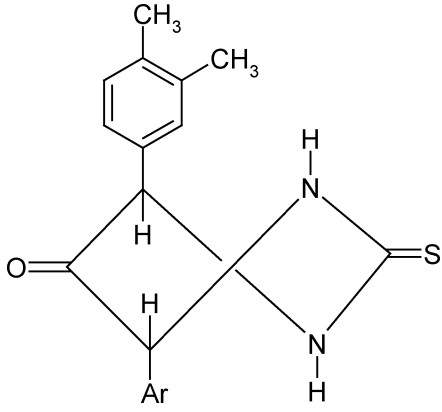


FIGURE 2 Twist boat form of compounds (**3**).

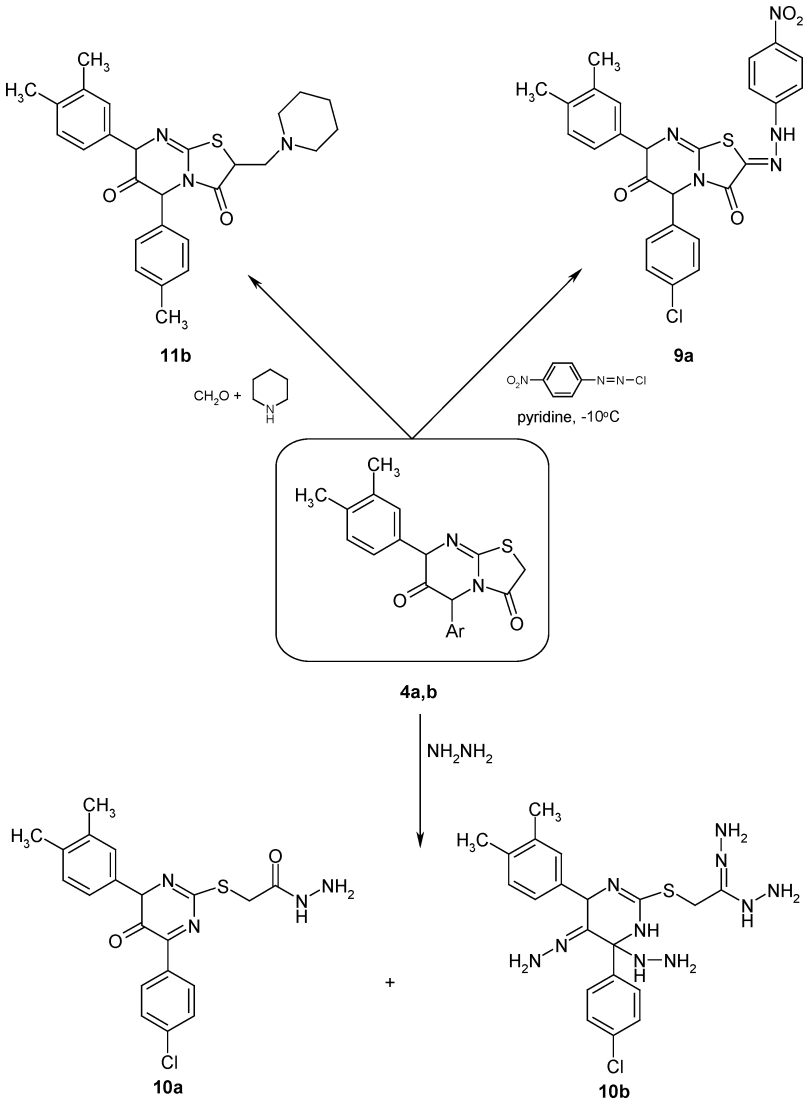
3,6-dione (**5a**) (Scheme 1). The latter compounds were prepared by new method in which 2-bromopropionic acid was used as a cyclocondensation reagent in dioxane.[12] This method is very easy to give compounds identical in all aspects with compound (**5a**). Elemental analysis of compound (**5a**) as well as its spectral data is compatible with the proposed structures (c.f., Experimental section).

The presence of an active methylene group in compounds (**4**) could be confirmed by condensation with aldehyde in acetic acid/acetic anhydride mixture in the presence of anhydrous sodium acetate to produce 7-(3,4-dimethyl-phenyl)-5-aryl-2-[aryl-methylidene]-tetrahydro-7*H*-thiazolo[3,2-*a*]pyrimidine-3,6-diones (**6**) (Scheme 1). Compounds (**6)** gave agreeable data in elemental analysis and spectral data (c.f., Experimental section). Compounds (**6**) could be directly prepared from compounds (**3**) in one step. Thus heating compound (**3a**) with bromoacetic acid and aromatic aldehyde in acetic acid/acetic anhydride mixture in the presence of sodium acetate gave product identical in all aspects with compound (**6a**) (m.p., mixed m.p., IR, MS, and ^{1}H NMR).

Compounds (**3**) are present in equilibrium with their 2-mercapto tautomers; they are expected to yield a mixture of two types of products when alkylated, but under experimental condition of Mannich, we could isolate only the 3-substituted product which proved to possess structure of compounds (**7**). Thus compounds (**3**) reacted with formaldehyde in the presence of piperidine to give the corresponding Mannich bases namely 6-(4-chloro-phenyl)-4-(3,4-dimethyl-phenyl)-1-piperidin-1-ylmethyl-2-thioxo-tetrahydro-pyrimidin-5-one (**7a**) and 4-(3,4-dimethyl-phenyl)-1-piperidin-1-ylmethyl-2-thioxo-6-*p*-tolyl-tetrahydro-pyrimidin-5-one (**7b**) successively (Scheme 1). The site of the attack was reached by the study of the IR as well as the ^{1}H NMR and mass spectrum. Thus the IR spectrum of compound (**7b)** showed the characteristic absorption bands at 1719.8, 1262.6, and 3293.4 for C=O, C=S, and NH groups successively. Its mass spectrum showed the molecular ion peak at *m/z* 422 (3.3%) supporting its molecular formula, and ^{1}H NMR spectrum agreed with the proposed structure (c.f., Experimental section).

Additionally, when compound (**3a)** were glycosidated by coupling with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosylbromide (α-ABG) in the presence of triethyl amine, it gave 4-(4-chloro-phenyl)-6-(3,4-dimethyl-phenyl)-1,3-di-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thioxo-tetrahydro-pyrimidin-5-one (**8a**) (Scheme 1), as the only isolable one product as judged by *Tlc* analysis. The structure of the new product was established according to its microanalytical and spectroscopic data. Its IR spectrum reveals the disappearance of (2 NH groups) as well as the existence of (C=S group) at 1225.6 cm^{-1} (c.f. Experimental section).

Compound (**4a**) coupled with aryldiazonium salt in pyridine to give 7-(3,4- dimethyl-phenyl)-5-(4-chloro-phenyl)-2-(4-nitrophenyl-hydrazono)-tetrahydro-7*H*-thiazolo [3,2-a]pyrimidine-3,6-dione (**9a**) (Scheme 2). Compound (**9a**) gave corrected value in elemental analysis as well as compatible spectroscopic data (c.f., Experimental section).



SCHEME 2

Interaction of compound (**4a**) with hydrazine hydrate afforded a product its MS revealed two compounds one has m/z ($M^+ = 414$) attributed to (**10a**) and the other compound has m/z ($M^+ = 475$) attributed to (**10b**) in which hydrazine hydrate reacted with (**10a**) *via* addition and condensation reactions. Further purification using colum chromatography, we could isolate only (**10a**) as pure compound. The structure of the new product was established according to its microanalytical and spectroscopic data (Scheme 2) (c.f., Experimental section).

Also compound (**4b**) reacted with formaldehyde in the presence of piperidine to give 7-(3, 4-dimethyl-phenyl)-2-piperidin-1-ylmethyl-5-*p*-tolyl-tetrahydro-7*H*- thiazolo [3,2-a]pyrimidine-3,6-dione (**11b**) (Scheme 2). Elemental analysis of compound (**11b**) as well as its spectroscopic data is compatible with the proposed structure (c.f. Experimental section).

ANTICANCER EVALUATION

Five selected new compounds (**3a**), (**3b**), (**6a**), (**6b**), and (**6c**) were tested for cytotoxic activity against the MCF_7 (Breast Carcinoma Cell Line) and H460 (Lung Carcinoma Cell Line). All tested new compounds were dissolved in DMSO in different concentrations (0, 1, 2, 5, and 10 μg/ml). Preliminary experiments were made using the human tumour cell line to identify the cytotoxicity of the selected compounds according to Skehan et al.[13]

Measurement of Potential Cytotoxicity by Sulforhodamine B. (SRB) Assay

- Cells were plated in 96 multiwell plates (10^4 cells/ well) for 24 h before treatment with the compounds to allow attachment of cell to the wall of the plate.
- Different concentrations of the compounds (1, 2.5, 5, and 10 μg/ml) were added to the cell monolayer.
- Triplicate wells were prepared for each individual dose.
- Monolayer cells were incubated with the compounds for 48 h at 37°C and in atmosphere of 5% CO_2.
- After 48 h, cells were fixed, washed and stained with SRB stain.
- Excess stain was washed with acetic acid and attached stain was recovered with tris EDTA buffer.
- Color intensity was measured in an ELISA Reader.
- The relation between surviving fraction and drug concentrations was plotted to get the survival curve of each tumor cell line of the specified compound Skehan et al.[13]

Results

All tested compounds were proven to have no cytotoxic activity (not active) against the MCF_7 and H460 at the chosen drug concentrations; see Chart 1 and 2, respectively.

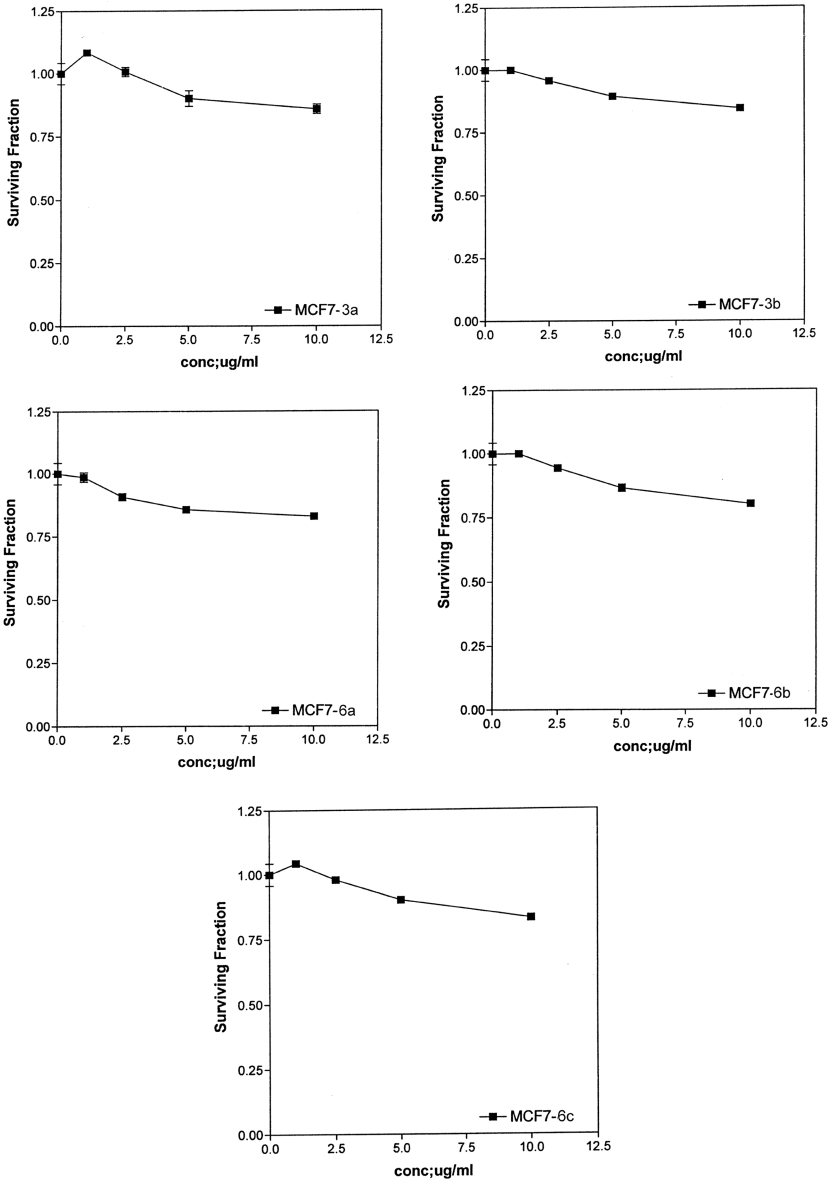


CHART 1

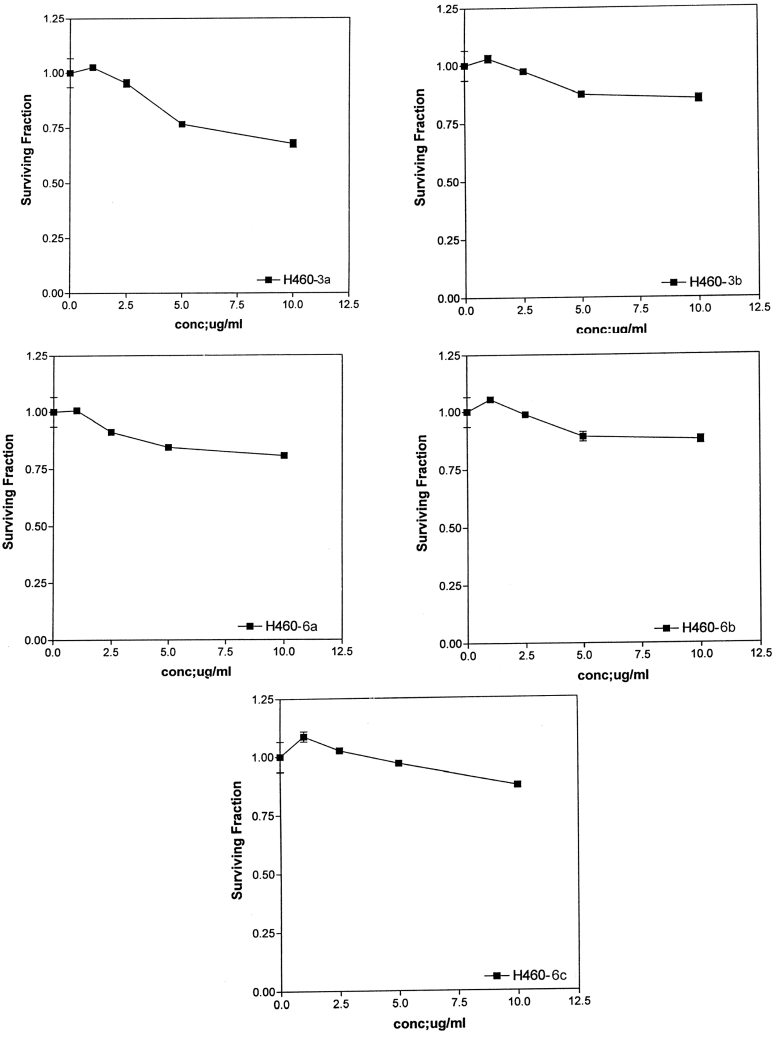


CHART 2

*The new compounds tested for anticancer activity in the Cairo University, National Cancer Institute, Cancer Biology Department, Cairo, Egypt.

BIOLOGICAL EVALUATION

Antibacterial Activity

Result of the minimum inhibitory concentration (MIC) test against *Escherichia coli* (Gram-negative bacteria) were not very promising,

compound (**6c**) out of **12** compounds displayed MIC in range of about 90 μg/ml, while the other tested compounds were generally inefficient (MIC >100 μg/ml) for each of bacteria and fungi.

Antifungal Activity

The prepared compounds **12** were evaluated in vitro against two strains of fungi, *Candida albicans* and *Aspergillus fumigates*, the most clinically fungi responsible for the majority of systemic fungi infections.

Result of (MIC) test against *Aspergillus fumigates* were not very promising, one compound out of **12** displayed MIC in range of about 50 μg/ml, while the rest of the series were generally inefficient (MIC >100 μg/ml).

Also, the result of (MIC) test against *Candida albicans* were not very promising, two compounds out of **12** displayed MIC in range of about 20 μg/ml, while the rest of the series were generally inefficient (MIC >100 μg/ml).

The different concentrations are produced by dilution (using the serial discontinuous concentration method). The MIC was readed as the smallest concentration of tested compound or control in series that prevent the development of visible growth of the test organism.[14] The MIC values (μg/ml) of tested compounds together with their structures are illustrated in Table I.

TABLE I In Vitro Antimicrobial Activity (MIC) of Tested Compounds

	Microorganism		
Tested compounds and references	*Eschericha coli*	*Aspergillus fumigates*	*Candida albicans*
Colimex	1μg/ml	>100	>100
Floconazole	—	—	—
2a	>100	>100	>100
2b	>100	>100	>100
3a	>100	>100	>100
3b	>100	>100	>100
4a	>100	50	20
4b	>100	>100	>100
6a	>100	> 100	>100
6b	>100	>100	>100
6c	90	>100	>100
7b	>100	>100	>100
9a	>100	>100	20
11b	>100	>100	>100

CONCLUSION

The tested compounds were evaluated in vitro against one strains of Gram-negative bacteria (*Escherichia coli*.) and two strains of fungi, *Aspergillus fumigates* and *Candida albicans,* Colimex, and Floconazole were used as references. Compound (**6c**) exerted significant antibacterial activity against *Escherichia coli* in range of 90 μg/ml while the rest of the compounds were generally inefficient (MIC >100 μg/ml). On the other hand, compound (**4a**) showed antifungal activity against *Aspergillus fumigates* in range of 50 μg/ml. Also compounds **(4a)** and (**9a)** exerted significant antifungal activity against *Candida albicans* in range of 20 μg/ml, while the rest of the compounds were generally inefficient (MIC >100 μg/ml) against each of*Aspergillus fumigates* and *Candida albicans*.

EXPERIMENTAL

All melting points are uncorrected and were measured using an Electrothermal IA 9100 apparatus. Analytical data were performed by Vario El Mentar apparatus, organic microanalysis section, National Research Centre. Their results were found to be in agreement with the calculated values (± 0.5). The IR spectra (KBr) were recorded on a Pye Unicam Sp-3-300 and Shimadzu FTIR 8101 PC infrared spectrophotometer. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in dimethylsulphoxide (DMSO-d_6). Chemical shifts are quoted in δ and were related to that of the solvents. The Mass spectra were recorded on a Shimadzu GCMS-QP-1000EX mass spectrometer at 70 ev.

Compound **1** was prepared according to method reported in literature.[9]

[3-(4-Chloro-phenyl)-oxiranyl]-(3,4-dimethyl-phenyl)-methanone (2a)

Hydrogen peroxide (5 ml, 30%) was added portion wise to a mixture of 3-(4-chloro-phenyl)-1-(3,4-dimethyl-phenyl)-propenone (**1a**) (0.01 mol) in acetone (50 ml), and methanol (15 ml) containing NaOH (1 g) at 20–25°C with stirring. The reaction mixture was left over night, cold water was added and the precipitated solid was filtered off, washed with cold water and crystallized from ethanol to give compound (**2a)** in 85% yield; m.p 96–97°C. IR spectrum (KBr, ν, cm^{-1}): 1655 (C=O); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 2.27 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 4.13

(s, 1H, epoxy-H), 4.80 (s, 1H, epoxy-H), 7.300–7.780 (m, 7 H, Ar-H); MS, *m/z* (%): 286 (M^+, 41.02), 133 (100). Analysis for $C_{17}H_{15}O_2Cl$ (286.5): required C, 71.20; H, 5.27; found C, 71.22; H, 5.29.

(3,4-Dimethyl-phenyl)-(3-*p*-tolyl-oxiranyl)-methanone (2b)

Hydrogen peroxide (5 ml, 30%) was added portion wise to a mixture of 1-(3,4-dimethyl-phenyl)-3-*p*-tolyl-propenone (**1b**) (0.01 mol) in acetone (50 ml), and methanol (15 ml) containing NaOH (1 g) at 20–25°C with stirring. The reaction mixture was left over night, cold water was added, and the precipitated solid was filtered off, washed with cold water, and crystallized from ethanol to give compound (**2b**) in 80% yield; m.p. 80°C IR spectrum (KBr, ν, cm^{-1}): 1724.7 (C=O); MS, *m/z* (%): 266 (M^+, 53.25), 242 (100). Analysis for $C_{18}H_{18}O_2$ (266): required C, 81.17; H, 6.81; found C, 81.30; H, 6.77.

Synthesis of (3a) and (3b)

A mixture of compounds (**2**) (0.01 mol) and thiourea (0.01 mol) 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 the proper solvent to give compounds (**3a**) and (**3b**).

4-(4-Chloro-phenyl)-6-(3,4-dimethyl-phenyl)-2-thioxo-tetrahydro-pyrimidin-5-one (3a)

From acetic acid, yield 72%, m.p. 137°C. IR spectrum (KBr, ν, cm^{-1}): 3128 (2NH), 1245.7 (C=S), 1757 (C=O);^{1}H NMR spectrum (DMSO-d_6, δ ppm): 2.22 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.047 (d, 1H, pyrimidine-H), 3.493 (d, 1H, pyrimidine-H), 7.187–7.377 (m, 7 H, Ar-H), 10.663 (s, 1H, NH, D_2O exchangeable), 11.478 (s, 1H, NH, D_2O exchangeable); MS, *m/z* (%): 344 (M^+, 13.23), 132 (100). Analysis for $C_{18}H_{17}N_2OSCl$ (344.5): required C, 62.69; H, 4.97; N, 8.12; S, 9.28; found C, 62.70; H, 4.98; N, 8.11; S, 9.01.

4-(3,4-Dimethyl-phenyl)-2-thioxo-6-*p*-tolyl-tetrahydro-pyrimidin-5-one (3b)

From benzene, yield 68%; m.p. 170°C. IR spectrum (KBr, ν, cm^{-1}): 3292, 3181 (2NH), 1263.5 (C=S), 1725 (C=O);^{1}H NMR spectrum (DMSO-d_6, δ ppm): 2.22 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.006 (d, 1H, pyrimidine-H), 3.386 (d, 1H, pyrimidine-H), 7.068–7.359 (m, 7H, Ar-H), 10.638 (s, 1H, NH, D_2O exchangeable), 11.378 (s, 1H, NH, D_2O exchangeable);^{13}C-NMR spectrum (DMSO-d_6, δ ppm): 42.892 and

71.480 SP^3 carbon, 122.792–136.506 aromatic carbons, 175.891 C=S, 181.417 C=O. MS, *m/z* (%): 324 (M^+, 38.9), 219 (100). Analysis for $C_{19}H_{20}N_2OS$ (324): required C, 70.34; H, 6.25; N, 8.63; S, 9.88; found C, 70.30; H, 6.25; N, 8.50; S, 9.50.

Synthesis of (4a) and (4b)

Method A

A mixture of compounds (**3)** (0.01 mol) with bromoacetic acid (0.01 mole) in acetic acid (30 ml)/acetic anhydride (15 ml) mixture in the presence of fused anhydrous sodium acetate (2 g) was refluxed for 3 h. 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 compounds (**4a**) and (**4b**).

Method B

A mixture of compounds (**3**) (0.01 mol) with bromoacetic acid (0.01 mol) in dioxane was refluxed for 3 h. The solvent was evaporated and the formed precipitate was filtered off and recrystallized from acetic acid to give compounds identical in all aspects with compounds obtained from method A.

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

Yield 65%; m.p. 146°C. IR spectrum (KBr, ν, cm^{-1}): 1720 (C=O), 1743(C=O);^{1}H NMR spectrum (DMSO-d_6, δ ppm): 2.21 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.549 (d, 1H, pyrimidine-H), 3.749 (d, 1H, pyrimidine-H), 4.457 (d, 1H, thiazole-H), 4.568 (d, 1H, thiazole-H), 6.935–7.665 (m, 7H, Ar-H); MS, *m/z* (%): 384 (M^+, 19.61), 132 (100). Analysis for $C_{20}H_{17}N_2O_2SCl$ (384.5): required C, 62.41; H, 4.45; N, 7.28; S, 8.33; found C, 62.50; H, 4.60; N, 7.20; S, 8.20.

7-(3,4-Dimethyl-phenyl)-5-*p*-tolyl-tetrahydro-7H-thiazolo [3,2-*a*]pyrimidine-3,6-dione (4b)

Yield 62%; m.p. 185°C. IR spectrum (KBr, ν, cm^{-1}): 1720 (C=O), 1740(C=O);Analysis for $C_{21}H_{20}N_2O_2S$ (364): required C, 69.21; H, 5.53; N, 7.69; S, 8.30; found C, 68.90; H, 5.54; N, 7.70; S, 8.38.

Synthesis of (5a)

Method A

A mixture of compound (**3a**) (0.01 mol) with 2-bromopropionic acid (0.01 mol) in acetic acid (30 ml)/acetic anhydride (15 ml) mixture in

the presence of fused anhydrous sodium acetate (2 g) was refluxed for 3 h. The solution was cooled, gradually poured onto cold water, and the formed precipitate was washed several times with water, filtered off, and recrystallized from ethanol to give compound (**5a**).

Method B

A mixture of compound (**3a)** (0.01 mole) with 2-bromopropionic acid (0.01 mole) in dioxane was refluxed for 3 h. The solvent was evaporated, and the formed precipitate was filtered off and recrystallized from acetic acid to give compound identical in all aspects with compound obtained from method A.

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

Yield 63%; m.p. 132°C. IR spectrum (KBr, ν, cm^{-1}): 1700 (C=O), 1756.5 (C=O); ^1H NMR spectrum (DMSO-d_6, δ ppm): 1.604 (d, 3H, CH_3), 2.238 (s, 3H, CH_3), 2.247 (s, 3H, CH_3), 3.058 (d, 1H, pyrimidine-H-7), 3.416 (d, 1H, pyrimidine-H-5), 4.441 (q, 1H, thiazole-H), 7.097–7.332 (m, 7H, Ar-H); MS, *m/z* (%): 383 (M^+-15, 23.99), 125 (100). Analysis for $C_{21}H_{19}N_2O_2SCl$ (398.5): required C, 63.23; H, 4.87; N, 7.18; S, 8.03; found C, 63.22; H, 4.77; N, 7.17; S, 8.00.

Synthesis of (6a–c)

Method A

A mixture of compounds (**4**) (0.01 mole) and equimolar amount of the corresponding aromatic aldehyde in acetic anhydride (30 ml) was refluxed for 3 h. The solution was cooled, gradually poured onto cold water and the formed precipitate was filtered off and recrystallized from the proper solvent to give compounds (**6a–c**).

Method B

A mixture of compounds (**3)** (0.01 mol), bromoacetic acid (0.01 mol), equimolar amount of the corresponding aromatic aldehyde in acetic acid (30 ml)/acetic anhydride (15 ml) mixture in the presence of fused anhydrous sodium acetate (2 g) was refluxed for 3 h. The solution was cooled, gradually poured onto cold water and the formed precipitate was washed several times with water, filtered off, and recrystallized from the proper solvent to give compounds identical in all aspects with compounds obtained from method A.

5-(4-Chloro-phenyl)-7-(3,4-dimethyl-phenyl)-2-[4-floro-phenyl-methylidene]-tetrahydro-7*H*-thiazolo [3,2-*a*] pyrimidine-3,6-dione (6a)

From: benzene/pet. ether, yield 73%; m.p. 190°C. IR spectrum (KBr, ν, cm^{-1}): 1702.7 (C=O), 1737.3 (C=O); Analysis for $C_{27}H_{20}FN_2O_2SClF$ (490.5): required C, 66.05; H, 4.07; N, 5.70; S, 6.52; found C, 66.05; H, 4.07; N, 5.75; S, 6.60.

7-(3,4-Dimethyl-phenyl)-5-*p*-tolyl-2-[4-methoxy-phenyl-methylidene]-tetrahydro-7*H*-thiazolo[3,2-*a*]-pyrimidine-3,6-dione (6b)

From: pet. Ether as an eluent on silica gel column chromatography, yield 60%; oil. IR spectrum (KBr, ν, cm^{-1}): 1703 (C=O), 1757.4 (C=O); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 2.215 (s, 3H, CH_3), 2.245 (s, 3H, CH_3), 2.309 (s, 3H, CH_3), 3.549 (d, 1H, pyrimidine-H), 3.749 (d, 1H, pyrimidine-H), 3.908 (s, 3H, OCH_3), 6.935–7.665 (m, 7H, Ar-H), 9.974 (s, 1H, exocyclic vinylic-H);[15] MS, *m/z* (%): 482 (M^+, 75.14), 105 (100). Analysis for $C_{29}H_{26}N_2O_3S$ (482): required C, 79.45; H, 5.43; N, 6.34; S, 7.30; found C, 79.55; H, 5.66; N, 6.29; S, 7.30.

7-(3,4-Dimethyl-phenyl)-5-*p*-tolyl-2-[4-floro-phenyl-methylidene]-tetrahydro-7*H*-thiazolo[3,2-*a*]-pyrimidine-3,6-dione (6c)

From: benzene/pet. ether, yield 68%; m.p. 210°C. IR spectrum (KBr, ν, cm^{-1}): 1700 (C=O), 1726.2 (C=O); MS, *m/z* (%): 456 (M^+-14, 3); Analysis for $C_{28}H_{23}N_2O_2SF$ (470): required C, 71.64; H, 4.90; N, 5.97; S, 6.83; found C, 71.54; H, 4.70; N, 5.23; S, 6.45.

Synthesis of (7a) and (7b)

Formaldehyde (1 ml, 40%) was added to compounds (**3**) (0.01 mol) in anhydrous ethanol (30 ml) the reaction mixture was heated for 5 minutes, then piperidine (0.01 mole) was added to the cold solution and the reaction mixture was stirred for 3 h at room temperature**.** The formed solid filtered off and recrystallized from ethanol to give compounds (**7a**) and (**7b**).

6-(4-Chloro-phenyl)-4-(3,4-dimethyl-phenyl)-1-piperidin-1-ylmethyl-2-thioxo-tetrahydro-pyrimidine-5-one (7a)

Yield 83%; m.p. 215°C. IR spectrum (KBr, ν, cm^{-1}): 3279.3 (NH), 1287.3 (C=S), 1723.9 (C=O);^{1}H NMR spectrum (DMSO-d_6, δ ppm): 1.201–1.458 (m, 6H, piperidine-H), 1.974 (t, 4H, piperidine-H), 2.216 (s, 3H,

CH_3), 2.249 (s, 3H, CH_3), 3.105 (d, 1H, pyrimidine-H), 3.489 (d, 1H, pyrimidine-H), 4.181 (d, 1H, CH_2), 4.57 (d, 1H, CH_2), 7.183–7.378 (m, 7H, Ar-H), 10.99 (s, 1H, NH, D_2O exchangeable). MS, *m/z* (%): 441 (M^+, 1.5), 98 (100). Analysis for $C_{24}H_{28}N_3OSCl$ (441): required C, 65.21; H, 6.38; N,9.51; S, 7.25; found C, 65.30; H, 6.40; N,9.70; S, 7.30.

4-(3,4-Dimethyl-phenyl)-1-piperidin-1-ylmethyl-2-thioxo-6-p-tolyl-tetrahydro-pyrimidin-5-one (7b)

Yield 79%; m.p. 205°C. IR spectrum (KBr, ν, cm^{-1}): 3293 (NH), 1283.5 (C=S), 1719 (C=O);^{1}H NMR spectrum (DMSO-d_6, δ ppm): 1.097–1.246 (m, 6H, piperidine-H), 1.980 (t, 4H, piperidine-H), 2.214 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.247(s, 3H, CH_3), 3.058 (d, 1H, pyrimidine-H), 3.416 (d, 1H, pyrimidine-H), 4.212 (d, 1H, CH_2), 4.441 (d, 1H, CH_2), 7.097–7.332 (m, 7H, Ar-H). MS, *m/z* (%): 422 (M^++ 3.1), 98 (100). Analysis for $C_{25}H_{31}N_3OS$ (421): required C, 71.42; H, 7.38; N, 6.66; S, 7.61; found, 71.44; H, 7.40; N, 6.72; S, 7.66.

4-(4-Chloro-phenyl)-6-(3,4-dimethyl-phenyl)-1,3-di-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-2-thioxo-tetrahydro-pyrimidin-5-one (8a)

To a solution of compound (**3a**) (0.01 mol) in 1 ml triethylamine, a solution of 2,3,4,6-tetra-O-acetyl-α-glucopyranosyl bromide (0.02 mol) in 5 ml DMF was added then the reaction mixture was stirred for 8 h at room temperature, evaporated under reduced pressure at 40°C, the residue washed with distilled water, filtered off, dried to afford an oily product compound (**8a**), IR spectrum (KBr, ν, cm^{-1}): 1658 (C=O) and 1747 (C=O).^{1}H NMR spectrum (DMSO-d_6, δ ppm):1.980, 2.000, 2.023, 2.037, 2.050, 2.070, 2.082, 2.098 (8s, 24H, 8CH_3CO-), 2.223 (s, 3H, CH_3), 2.258 (s, 3H, CH_3), 3.047 (d, 1H, pyrimidine-H), 3.448 (d, 1H, pyrimidine-H) , 4.139-4.210 (m, 6H, 5′-H, 5″-H, 6′-H_2 , 6″-H_2), 4.742-4.923 (m, 7H, 2′-H, 2″-H, 3′-H, 3″-H, 4′-H, 4″-H, 1′-H), and 5.446 (d, 1H, 1″-H).[16]

5-(4-Chloro-phenyl)-7-(3,4-dimethyl-phenyl)-2-(4-nitrophenyl-hydrazono)-tetrahydro-7*H*-thiazolo [3,2-*a*]pyrimidin-3,6-dione (9a)

The aromatic amine (0.01 mol) was dissolved in concentrated hydrochloric acid (3 ml) and water (2 ml) cooled to −10°C and treated with sodium nitrate (0.7 g, 5 ml water). The diazotized amine was added gradually while stirring to cooled solution of compound **(4a)** (0.01 mol) in pyridine (20 ml). The reaction mixture was refrigerator for 1/2 h and then

diluted with water and recrystallized from benzene/pet. ether to give compound (**9a)** in 52% yield; m.p. 152°C. IR spectrum (KBr, ν, cm^{-1}): 3296.6 (NH), 1705 (C=O), 1771.4 (C=O);^{1}H NMR spectrum (DMSO-d_6, δ ppm): 2.238 (s, 3H, CH_3), 2.247 (s, 3H, CH_3), 3.058 (d, 1H, pyrimidine-H), 3.416 (d, 1H, pyrimidine-H) , 3.831 (s, 1H, NH, D_2O exchangeable), 7.097–7.332 (m, 11 H, Ar-H); MS, *m/z* (%): 533 (M^+, 40.7), 132 (100). Analysis for $C_{26}H_{20}N_5O_2SCl$ (533): C, 61.25; H, 4.59; N, 10.20; S, 5.84; found C, 61.00; H, 4.62; N, 10.22; S, 5.85.

4-(4-Chloro-phenyl)-6-(3,4-dimethyl-phenyl)-5,6-dihydropyrimidin-2-yl-thioacetylhydrazide (10a)

To a solution of compound (**4a**) (0.05 mol) in absolute ethanol (15 ml), hydrazine hydrate (98%) (0.06 mol) was added and the reaction mixture was refluxed for 2 h. The reaction mixture was cooled, poured into water, and the solid product formed was washed with little ethanol, filtered off, and chromatographed on silica gel column using pet. ether (60–80) as an eluent to give compound (**10a**) in 50% yield; m.p 196°C. IR spectrum (KBr, ν, cm^{-1}): 3286.3 (br $NHNH_2$), 1720.9 (C=O), 1651.1 (C=O);^{1}H NMR spectrum (DMSO-d_6, δ ppm): 2.223 (s, 3H, CH_3), 2.258 (s, 3H, CH_3), 3.047 (d, 1H, pyrimidine-H), 4.386 (s, 2H, NH_2, D_2O exchangeable), 5.139 (s, 2H, CH_2), 7.187–7.377 (m, 7H, Ar-H), 12.379 (s, 1H, NH, D_2O exchangeable). Analysis for $C_{20}H_{19}N_4O_2SCl$ (414): C, 57.97; H, 4.58; N, 13.52; S, 7.72; found C, 57.23; H, 4.33; N, 13.09; S, 7.60.

7-(3,4-Dimethyl-phenyl)-2-piperidin-1-ylmethyl-5-*p*-tolyl-tetrahydro-7H-thiazolo[3,2-*a*]pyrimidine-3,6-dione (11b)

Formaldehyde (1 ml, 40%) was added to compound **(4b)** (0.01 mol) in anhydrous ethanol (30 ml) the reaction mixture was heated for 5 minutes, then piperidine (0.01 mol) was added to the cold solution and the reaction mixture was stirred for 3 h at room temperature**.** The formed solid filtered off and recrystallized from ethanol to give compound (**11b)** in 55% yield; m.p. 210°C. IR spectrum (KBr, ν, cm^{-1}):1500.5 (C=N), 1705 (C=O), 1771 (C=O);^{1}H NMR spectrum (DMSO-d_6, δ ppm): 1.097–1.246 (m, 6H, piperidine-H), 1.980 (t, 4H, piperidine-H), 2.214 (s, 3H, CH_3), 2.238 (s, 3H, CH_3), 2.247 (s, 3H, CH_3), 3.058 (d, 1H, pyrimidine-H), 3.416 (d, 1H, pyrimidine-H), 4.323–4.408 (m, 1H, CH_2), 4.496–4.539 (m, 1H, CH_2), 5.030–5.120 (m, 1H, thiazole-H), and 7.097–7.332 (m, 7 H, Ar-H), MS, *m/z* (%): 406 (M^+-55, 3.2), 98 (100). Analysis for $C_{27}H_{31}N_3O_2S$ (461): required C, 70.28; H, 6.72; N, 9.11; S, 6.94; found C, 70.00; H, 6.11; N, 9.00; S, 6.55.

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