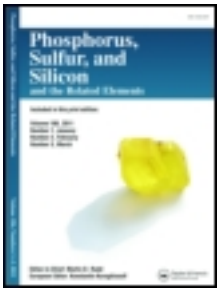

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Synthesis of Some New 1,2,3,4-Tetrahydropyrimidine-2-thiones and Their Thiazolo[3,2-a]pyrimidine Derivatives as Potential Biological Agents

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Synthesis of Some New 1,2,3,4-Tetrahydropyrimidine-2-thiones and Their Thiazolo[3,2-*a*]pyrimidine Derivatives as Potential Biological Agents

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Some new N-(4-chlorophenyl)-6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide ***4(a–h)*** *were synthesized by the reaction of N-(4-chlorophenyl)-3-oxobutanamide, thiourea and different aromatic aldehydes. The synthesis of N-(4-chlorophenyl)-7-methyl-5-aryl-2,3-dihydro-5H-thiazolol[3,2-a]pyrimidine-6-carboxamide* ***5(a–h)*** *was accomplished by cyclocondensation of 1,2,3,4-tetrahydropyrimidine-2-thiones* ***4(a–h)*** *and 1,2-dibromoethane. The structures of these compounds have been proved by IR, ^{1}H-NMR, and Mass spectral studies. Synthesized compounds* ***4(a–h)*** *and* ***5(a–h)*** *were evaluated for their antimicrobial activities. Some of the compounds exhibited significant inhibition on bacterial and fungal growth as compared to standard drugs.*

Keywords 1,2,3,4-Tetrahydropyrimidine-2-thiones; antimicrobial activity; spectral analysis; synthesis; thiazolo[3,2-*a*]pyrimidines

INTRODUCTION

The chemistry and the synthesis of 1,2,3,4-tetrahydropyrimidine-2-thiones have been attracting widespread attention in recent years. The present popularity of these tetrahydropyrimidines is mainly due to their close structural relationship to the clinically important dihydropyridine calcium channel blockers.[1–6] 1,2,3,4-tetrahydropyrimidine-2-thione is known as a versatile heterocyclic compound which has been

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subjected to a large variety of structural modifications in order to synthesize derivatives with different biological properties. Their various condensed derivatives are reported to possess calcium antagonist,[7–9] anti-inflammatory,[10–12] analgesic,[13] antitumor,[14,15] antidepressant,[16] antibacterial, and antifungal effects.[17–19] Several synthetic approaches have been reported for the synthesis of fused heterocyclic pyrimidine derivatives.[20–22]

Encouraged by this reports, in this study, synthesis and structural elucidation of *N*-(4-chlorophenyl)-6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide **4(a–h)** and *N*-(4-chlorophenyl)-7-methyl-5-aryl-2,3-dihydro-5*H*-thiazolol[3,2-*a*]pyrimidine-6-carboxamide **5(a–h)** are reported. The antibacterial activity against *Staphylococcus aureus* ATCC 6538, *Staphylococcus epidermidis* ATCC 12228, *Escherichia coli* ATCC 8739, *Pseudomonas aeruginosa* ATCC 1539, and antifungal activity against *Candida albicans* ATCC 10231 were investigated.

RESULTS AND DISCUSSION

Chemistry

Ethylacetoacetate suspended in toluene was refluxed with 4-chloroaniline in presence of catalytic amount of NaOH to give *N*-(4-chlorophenyl)-3-oxobutanamide **1**. IR spectrum displayed a definite absorption at 1690 cm^{-1} due to carboxamide group. Reaction of this with different aromatic aldehyde and thiourea using classical Biginelli reaction[23] yielded *N*-(4-chlorophenyl)-6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide **4(a–h)**. Condensation of **4(a–h)** with 1,2-dibromoethane in DMF led to the *N*-(4-chlorophenyl)-7-methyl-5-aryl-2,3-dihydro-5*H*-thiazolol[3,2-*a*]pyrimidine-6-carboxamide **5(a–h)**. The formulas of the compounds **4(a–h)** and **5(a–h)** were confirmed by the elemental analysis and their structures were determined by IR, ^{1}H NMR and EIMS spectral data.

The IR spectra of the compounds displayed the characteristics –C=O stretching vibration at 1720–1660 cm^{-1}. ^{1}H NMR spectrum of the compounds **4c** showed a broad singlet at 9.82 ppm due to –NH of carboxamide group and two broad singlets at 8.45 and 9.56 ppm due to –NH group of pyrimidine ring. At 5.44 ppm, a singlet appeared, due to the chiral proton of the fourth position. Therefore, the above discussion has supported the pyrimidine ring formation.

In compound **5c**, the absence of two broad singlet signals between 8–10 ppm and the presence of four multiplate signals between 3.08–3.26 ppm have proven that the ring formation took place between the

TABLE I Analytical Data of the Newly Prepared Compounds

Compd. no.	M.p.°C (solvent)	Color [yield (%)]	Mol. formula (mol. wt.)	Elemental analysis [calcd./found (%)]			
				C	H	N	S
4a	240–241 (Dioxane)	Yellowish white [46%]	$C_{20}H_{20}ClN_3O_3S$ (417.90)	57.48 (57.38)	4.82 (4.76)	10.05 (10.03)	7.67 (7.62)
4b	240–241 (Dioxane)	Off white [52%]	$C_{19}H_{18}ClN_3O_2S$ (387.88)	58.83 (58.76)	4.68 (4.66)	10.83 (10.79)	8.27 (8.23)
4c	235–236 (Dioxane)	White [48%]	$C_{19}H_{18}ClN_3O_2S$ (387.88)	58.83 (58.74)	4.68 (4.70)	10.83 (10.80)	8.27 (8.32)
4d	272–273 (Dioxane)	Yellowish white [53%]	$C_{18}H_{16}ClN_3OS$ (357.85)	60.41 (60.38)	4.51 (4.41)	11.74 (11.81)	8.96 (8.88)
4e	262–264 (Dioxane)	Pale yellow [41%]	$C_{18}H_{15}ClN_4O_3S$ (402.85)	53.67 (53.59)	3.75 (3.68)	13.91 (13.87)	7.96 (7.90)
4f	283–284 (Dioxane)	White [36%]	$C_{18}H_{16}ClN_3O_2S$ (373.85)	57.83 (57.87)	4.31 (4.32)	11.24 (11.19)	8.58 (8.65)
4g	281–282 (Dioxane)	White [35%]	$C_{18}H_{16}ClN_3O_2S$ (373.85)	57.83 (57.71)	4.31 (4.29)	11.24 (11.20)	8.58 (8.51)
4h	273–275 (Dioxane)	Yellowish white [41%]	$C_{18}H_{15}Cl_2N_3OS$ (392.30)	55.11 (55.00)	3.85 (3.91)	10.71 (0.68)	8.17 (8.20)
5a	199–200 (Ethanol)	Cream [77%]	$C_{22}H_{22}ClN_3O_3S$ (443.94)	59.52 (59.46)	4.99 (4.87)	9.47 (9.42)	7.22 (7.16)
5b	206–207 (Ethanol)	White [81%]	$C_{21}H_{20}ClN_3O_2S$ (413.92)	60.94 (60.89)	4.87 (4.78)	10.15 (10.06)	7.75 (7.66)
5c	222–223 (Ethanol)	Pale yellow [79%]	$C_{21}H_{20}ClN_3O_2S$ (413.92)	60.94 (60.88)	4.87 (4.78)	10.15 (10.21)	7.75 (7.88)
5d	205–206 (Ethanol)	White [82%]	$C_{20}H_{18}ClN_3OS$ (383.89)	62.57 (62.66)	4.73 (4.68)	10.95 (10.87)	8.35 (8.31)
5e	201–202 (Ethanol)	Yellowish white [69%]	$C_{20}H_{17}ClN_4O_3S$ (428.89)	56.01 (55.91)	4.00 (4.11)	13.06 (13.01)	7.48 (7.54)
5f	231–232 (Ethanol)	Pale yellow [89%]	$C_{20}H_{18}ClN_3O_2S$ (399.89)	60.07 (59.95)	4.54 (4.62)	10.51 (10.57)	8.02 (7.93)
5g	219–220 (Ethanol)	Pale Yellow [76%]	$C_{20}H_{18}ClN_3O_2S$ (399.89)	60.07 (60.01)	4.54 (4.47)	10.51 (10.43)	8.02 (8.09)
5h	214–216 (Ethanol)	White [80%]	$C_{20}H_{17}Cl_2N_3OS$ (418.33)	57.42 (57.36)	4.10 (4.17)	10.04 (10.06)	7.66 (7.62)

second and third positions of pyrimidine ring. The formation of compound **5c** was further supported by disappearance of the IR band at 1211 cm^{-1} due to the C=S group and appearance of a new band at 680 cm^{-1} due to the C-S-C bond. EIMS of all compounds were taken. MS of all compounds showed the molecular ion peak (M^+) with low intensity and other peak due to fragments that supported expected structures. Experiments were performed to evaluate the antibacterial activity against *Staphylococcus aureus* ATCC 6538, *Staphylococcus epidermidis* ATCC 12228, *Escherichia coli* ATCC 8739, *Pseudomonas aeruginosa* ATCC 1539, and antifungal activity against *Candida albicans* ATCC 10231 were investigated using the disk diffusion method (Table I).

Microbiology

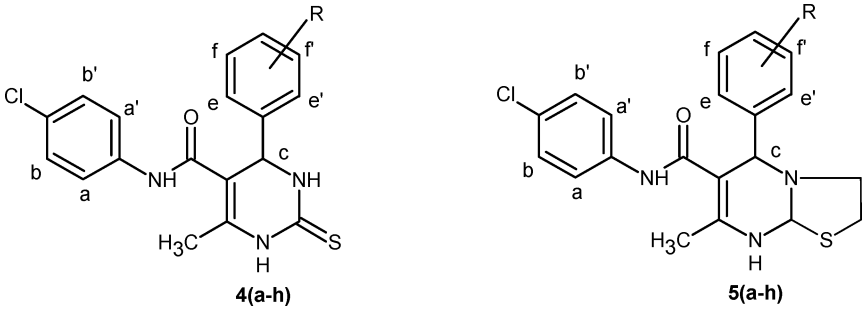
The in vitro antimicrobial activity of the synthesized compounds was tested against *S. aureus* ATCC 6538, *S. epidermidis* ATCC 12228, *E. coli* ATCC 8739, *P. aeruginosa* ATCC 1539, and *C. albicans* ATCC 10231 using the disk diffusion method where each disc contained 200 μg of the tested compound.[24]

For this method, Mueller-Hinto agar (Difco) was melted at 100°C and after cooing to 56°C, was poured into Petri plates of 9 cm diameter in quantities of 20 mL, and left on a flat surface to solidify; the surface of the medium was dried at 37°C. Then, the cultures of each bacteria and yeast strain—after being kept in Mueller-Hinton broth at 37°C for 18–24 h and diluted with Mueller-Hinton broth to 10^5 cfu/mL—were pipetted into the Mueller-Hinton agar plate prepared as described previously. The surface of the medium was allowed to dry. The 10000 μg/mL (in DMSO) compound impregnated discs were applied to the surface of inoculated plates. The Petri plates were placed in an incubator at 37°C. After 10–24 h of incubation, the Petri plates were examined. Evaluation of the new compounds established that compound **4e** in which a nitro group is present at the third position of the aryl ring, possess stronger antibacterial activity as compared to others. While compounds **4b, 4c,** and **4e** were active against *S. epidermidis* ATCC 12228; **4b, 4e,** and **4f** were active against E. *coli* ATCC 8739; and **4e** was active against *P. aeruginosa* ATCC 1539. In case of *C. albicans* ATCC 10231 compounds **4e** and **5e** showed a better activity than the others. Compounds **4a, 4b, 4f, 4g, 4h, 5c,** and **5e** exhibited moderate activities as compared to the standard against various microorganisms. It was also noticed that compounds **4(a–h)** demonstrated higher inhibitory activity than **5(a–h)** due to its free –C=S group (Table II).

TABLE II Antimicrobial Activity of the Synthesized Compounds 4(a–h) and 5(a–h)

Compound	*S. aureus*	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*C. albicans*
4a	12.0 $(0.40)^{C_1}$ $(0.42)^{C_2}$	17.5 $(0.67)^{C_1}$ $(0.77)^{C_2}$	14.2 $(0.67)^{C_1}$ $(0.61)^{C_2}$	17.8 $(0.63)^{C_1}$ $(0.66)^{C_2}$	18.5 $(0.74)^{C_1}$ $(0.80)^{C_2}$
4b	17.5 $(0.58)^{C_1}$ $(0.62)^{C_2}$	22.8 $(0.87)^{C_1}$ $(1.03)^{C_2}$	19.3 $(0.92)^{C_1}$ $(0.84)^{C_2}$	21.3 $(0.76)^{C_1}$ $(0.79)^{C_2}$	20.0 $(0.80)^{C_1}$ $(0.86)^{C_2}$
4c	14.3 $(0.47)^{C_1}$ $(0.51)^{C_2}$	21.0 $(0.80)^{C_1}$ $(0.95)^{C_2}$	14.0 $(0.67)^{C_1}$ $(0.61)^{C_2}$	20.0 $(0.71)^{C_1}$ $(0.74)^{C_2}$	16.3 $(0.65)^{C_1}$ $(0.70)^{C_2}$
4d	15.0 $(0.50)^{C_1}$ $(0.54)^{C_2}$	13.7 $(0.53)^{C_1}$ $(0.62)^{C_2}$	12.0 $(0.57)^{C_1}$ $(0.52)^{C_2}$	17.0 $(0.60)^{C_1}$ $(0.63)^{C_2}$	13.5 $(0.54)^{C_1}$ $(0.58)^{C_2}$
4e	22.9 $(0.76)^{C_1}$ $(0.82)^{C_2}$	26.0 $(1.0)^{C_1}$ $(1.18)^{C_2}$	20.0 $(0.95)^{C_1}$ $(0.87)^{C_2}$	24.5 $(0.87)^{C_1}$ $(0.91)^{C_2}$	22.5 $(0.90)^{C_1}$ $(0.97)^{C_2}$
4f	20.0 $(0.67)^{C_1}$ $(0.71)^{C_2}$	17.5 $(0.67)^{C_1}$ $(0.79)^{C_2}$	19.5 $(0.93)^{C_1}$ $(0.85)^{C_2}$	22.3 $(0.79)^{C_1}$ $(0.83)^{C_2}$	17.8 $(0.71)^{C_1}$ $(0.77)^{C_2}$
4g	23.3 $(0.78)^{C_1}$ $(0.83)^{C_2}$	19.2 $(0.74)^{C_1}$ $(0.87)^{C_2}$	18.0 $(0.86)^{C_1}$ $(0.78)^{C_2}$	22.6 $(0.79)^{C_1}$ $(0.84)^{C_2}$	12.0 $(0.48)^{C_1}$ $(0.52)^{C_2}$
4h	23.0 $(0.77)^{C_1}$ $(0.82)^{C_2}$	18.6 $(0.71)^{C_1}$ $(0.85)^{C_2}$	17.5 $(0.83)^{C_1}$ $(0.76)^{C_2}$	19.5 $(0.69)^{C_1}$ $(0.72)^{C_2}$	14.6 $(0.58)^{C_1}$ $(0.63)^{C_2}$
5a	11.2 $(0.37)^{C_1}$ $(0.40)^{C_2}$	9.5 $(0.37)^{C_1}$ $(0.43)^{C_2}$	10.0 $(0.48)^{C_1}$ $(0.43)^{C_2}$	14.3 $(0.51)^{C_1}$ $(0.53)^{C_2}$	17.8 $(0.71)^{C_1}$ $(0.77)^{C_2}$
5b	9.7 $(0.32)^{C_1}$ $(0.35)^{C_2}$	11.3 $(0.43)^{C_1}$ $(0.51)^{C_2}$	12.0 $(0.57)^{C_1}$ $(0.52)^{C_2}$	16.5 $(0.59)^{C_1}$ $(0.61)^{C_2}$	12.0 $(0.48)^{C_1}$ $(0.52)^{C_2}$
5c	14.0 $(0.47)^{C_1}$ $(0.50)^{C_2}$	13.0 $(0.50)^{C_1}$ $(0.59)^{C_2}$	13.5 $(0.64)^{C_1}$ $(0.59)^{C_2}$	18.2 $(0.65)^{C_1}$ $(0.67)^{C_2}$	18.5 $(0.74)^{C_1}$ $(0.80)^{C_2}$
5d	15.5 $(0.52)^{C_1}$ $(0.55)^{C_2}$	17.8 $(0.68)^{C_1}$ $(0.81)^{C_2}$	12.5 $(0.59)^{C_1}$ $(0.54)^{C_2}$	20.7 $(0.74)^{C_1}$ $(0.77)^{C_2}$	13.3 $(0.53)^{C_1}$ $(0.57)^{C_2}$
5e	21.2 $(0.70)^{C_1}$ $(0.75)^{C_2}$	18.5 $(0.71)^{C_1}$ $(0.84)^{C_2}$	17.5 $(0.83)^{C_1}$ $(0.76)^{C_2}$	20.0 $(0.71)^{C_1}$ $(0.74^{C_2}$	22.0 $(0.88)^{C_1}$ $(0.95)^{C_2}$
5f	18.0 $(0.60)^{C_1}$ $(0.64)^{C_2}$	9.5 $(0.36)^{C_1}$ $(0.43)^{C_2}$	14.6 $(0.61)^{C_1}$ $(0.63)^{C_2}$	14.0 $(0.50)^{C_1}$ $(0.51)^{C_2}$	12.0 $(0.48)^{C_1}$ $(0.52)^{C_2}$
5g	16.0 $(0.53)^{C_1}$ $(0.57)^{C_2}$	17.2 $(0.66)^{C_1}$ $(0.78)^{C_2}$	13.0 $(0.61)^{C_1}$ $(0.56)^{C_2}$	17.5 $(0.62)^{C_1}$ $(0.64)^{C_2}$	13.5 $(0.54)^{C_1}$ $(0.58)^{C_2}$
5h	18.6 $(0.62)^{C_1}$ $(0.66)^{C_2}$	17.5 $(0.67)^{C_1}$ $(0.79)^{C_2}$	14.6 $(0.69)^{C_1}$ $(0.63)^{C_2}$	17.5 $(0.62)^{C_1}$ $(0.64)^{C_2}$	14.0 $(0.56)^{C_1}$ $(0.60)^{C_2}$
$\mathbf{C_1}$	30	26	21	28	25
$\mathbf{C_2}$	28	22	23	27	23

Zone of Inhibition (mm) $(\text{activity index})^{\text{std}}$. Activity index = Inhibition zone of the sample/Inhibition zone of the standard. For antibacterial activity: $\mathbf{C_1}$ = Ciprofloxacin & $\mathbf{C_2}$ = Gentamicin. For antifungal activity: $\mathbf{C_1}$ = Griseofulvin & $\mathbf{C_2}$ = Gentamicin.



SCHEME 1

EXPERIMENTAL SECTION

General Procedures

Melting points were estimated in open capillaries and are uncorrected. Elemental analyses were performed on a Carlo Erba EA 1108 elemental analyzer. IR spectra were recorded on KBr discs, using an FTIR-8400 Spectrophotometer. ^{1}H NMR spectra were taken on a Bruker AVANCE II 400 (^{1}H: 400 Mz, [d_6] DMSO) Spectrometer. Mass spectra were determined using direct inlet probe on a GCMS-QP2010 mass spectrometer (Shimadzu). Reactions were monitored on Merck aluminum thin layer chromatography (TLC, UV_{254nm}) pates. Visualization was accomplished either on UV chamber or in Iodine vapor. Column chromatography was carried out on silica gel (60–120 mesh, Merck chemicals).

Synthesis of *N*-(4-chlorophenyl)-3-oxobutanamide (1)

A suspension of ethylacetoacetate (0.01 mol) and 4-choloro aniline (0.01 mol) in toluene (50 ml) containing catalytic amount (0.05 ml, 40%) of NaOH was reflux on oil bath for 8 h. After completion of the reaction (TLC monitoring), the solvent was removed under reduced pressure, separated solid was filtered, washed with petroleum ether and crystallized from ethanol to give **1**.

General procedure of synthesis of N-(4-chlorophenyl)-6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4a–h)

A mixture of *N*-(4-chlorophenyl)-3-oxobutanamide (0.01 mol), different aromatic aldehyde (0.01 mol), thiourea (0.01 mol), and ethanol (8 ml), containing 0.4 ml of concentrated HCl was heated under reflux for 6–8 h. The solution was allowed to stand at −20°C for several

hours and precipitation was observed. The products were isolated as crystalline powder **4a**–**h**.

N-(4-chlorophenyl)-6-methyl-4-(3,4-dimethoxyphenyl)-2-thioxo-1,2,3,4-tetrahyd-ropyrimidine-5-carboxamide (4a)

IR (ν_{max} cm^{-1}, KBr): 3368 (N-H str.), 1678 (C=O str.), 1215 (C=S str.), 765 (C-Cl str.). ^{1}H NMR 400 Mz ($CDCl_3$+ DMSO d_6): 2.14 (s, 3H, -CH_3), 3.75 (s, 3H, -OCH3), 3.78 (s, 3H, -OCH_3, 5.45 (s, 1H, Ar-Hc), 6.81–6.90 (m, 3H, Ar-H), 7.18–7.20(d, 2H, Ar-Hb-b' J = 8.44Hz), 7.56–7.58(d, 2H, Ar-Ha-a' J = 8.48Hz) 9.24(s, 1H, -NH pyrimidine), 9.60 (s, 1H, -NH pyrimidine), 9.80 (s, 1H, -NH amide). EI^+ m/z: 419 (M+2), 417, 402, 386, 357, 291, 259, 232, 208, 191, 176, 153, 127.

N-(4-chlorophenyl)-6-methyl-4-(4-methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxamide (4b)

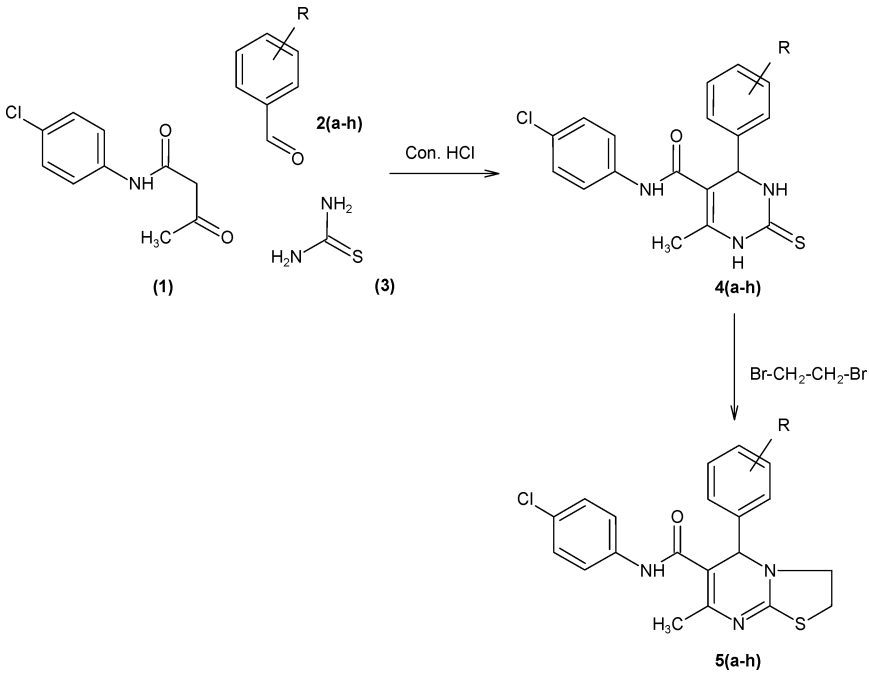
IR (ν_{max} cm^{-1}, KBr): 3396 (N-H str.), 1683 (C=O str.) 1213 (C=S str.), 756 (C-Cl str.). ^{1}H NMR 400 Mz ($CDCl_3$+ DMSO d_6): 2.13 (s, 3H, -CH_3), 3.74 (s, 3H, -OCH3), 5.43 (s, 1H, Ar-Hc), 6.81–6.64 (dd, 2H, Ar-Hf-f' J = 11.44Hz), 7.16–7.20 (d, 2H, Ar-Hb-b' J = 7.12Hz), 7.22–7.27(dd, 2H, Ar-He-e' J = 11.8Hz), 7.53–7.57(dd, 2H, Ar-Ha-a' J = 7.04Hz) 9.23(s, 1H, -NH pyrimidine), 9.56 (s, 1H, -NH pyrimidine), 9.83 (s, 1H, -NH amide). EI^+ m/z: 387, 357, 261, 233, 202, 178, 161, 153, 127, 90, 67.

N-(4-chlorophenyl)-6-methyl-4-(2-methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxamide (4c)

IR (ν_{max} cm^{-1}, KBr): 3383 (N-H str.), 1683 (C=O str.) 1211 (C=S str.), 732 (C-Cl str.). ^{1}H NMR 400 Mz ($CDCl_3$+ DMSO d_6): 2.14 (s, 3H, -CH_3), 3.74 (s, 3H, -OCH3), 5.44 (s, 1H, Hc), 6.87–7.59 (m, 8H, Ar-H, J = 7.6Hz), 8.45 (s, 1H, -NH pyrimidine), 9.56 (s, 1H, -NH pyrimidine), 9.82 (s, 1H, -NH amide). EI^+ m/z: 387, 356, 261, 233, 202, 178, 155, 136, 91, 67.

N-(4-chlorophenyl)-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4d)

IR (ν_{max} cm^{-1}, KBr): 3376 (N-H str.), 1704 (C=O str.) 1211 (C=S str.), 743 (C-Cl str.). ^{1}H NMR 400 Mz ($CDCl_3$+ DMSO d_6): 2.14 (s, 3H, -CH_3), 5.50 (s, 1H, Ar-Hc), 7.17–7.19(dd, 2H, Ar-Hb-b' J = 6.92Hz), 7.20–7.34(m, 5H, Ar-H), 7.53–7.57(dd, 2H, Ar-Ha-a' J = 6.96Hz), 9.22 (s, 1H, -NH pyrimidine), 9.5636 (s, 1H, -NH pyrimidine), 9.85 (s, 1H, -NH amide). EI^+ m/z: 357, 342, 280, 231, 216, 172, 144, 131, 103, 91, 67.



Where R = 3,4-$(OCH_3)_2$, 4-OCH_3, 2-OCH_3, 3-NO_2, 3-OH, 2-OH, 2-Cl

SCHEME 2

N-(4-chlorophenyl)-6-methyls-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyri-midine-5-carboxamide (4e)

IR (ν_{max} cm^{-1}, KBr): 3408 (N-H str.), 1683 (C=O str.) 1218 (C=S str.), 736 (C-Cl str.)^{1}H NMR 400 Mz ($CDCl_3$+ DMSO d_6): 2.20 (s, 3H, -CH_3), 5.59 (s, 1H, Ha), 7.17–8.25 (m, 8H, Ar-H, J = 6.96Hz), 9.51 (s, 1H, -NH pyrimidine), 9.72 (s, 1H, -NH pyrimidine), 10.87 (s, 1H, -NH amide). EI^+ m/z: 402, 385, 357, 276, 217, 176, 153, 127, 102, 90, 67.

N-(4-chlorophenyl)-6-methyl-4-(3-hydroxyphenyl)-2-thioxo-1,2,3,4-tetrahydropy-rimidine-5-carboxamide (4f)

IR (ν_{max} cm^{-1}, KBr): 3406 (N-H str.), 1718 (C=O str.) 1210 (C=S str.), 744 (C-Cl str.). ^{1}H NMR 400 Mz ($CDCl_3$+ DMSO d_6): 2.15 (s, 3H, -CH_3), 5.44 (s, 1H, Ar-Hc), 6.72–7.14 (m, 4H, Ar-H), 7.16–7.20 (dd, 2H, Ar-Hb-b' J = 6.96Hz), 7.47–7.52 (dd, 2H, Ar-Hb-b' J = 7.04Hz) 8.78 (s, 1H, -NH pyrimidine), 9.11 (s, 1H, -NH pyrimidine), 9.46 (s, 1H, -NH amide). EI^+ m/z: 373, 313, 247, 220, 188, 160, 147, 127, 99, 91, 65.

N-(4-chlorophenyl)-6-methyl-4-(2-hydroxyphenyl)-2-thioxo-1,2,3,4-tetrahydrop-yrimidine-5-carboxamide (4g)

IR (ν_{max} cm^{-1}, KBr): 3406 (N-H str.), 1718 (C=O str.) 1210 (C=S str.), 723 (C-Cl str.). ^{1}H NMR 400 Mz ($CDCl_3$+ DMSO d_6): 1.81 (s, 3H, -CH_3), 4.65 (s, 1H, Ar-Hc), 6.77–7.62 (m, 8H, Ar-H), 9.97 (s, 1H, -NH pyrimidine), 9.05 (s, 1H, -NH pyrimidine), 10.22 (s, 1H, -NH amide). EI^+ m/z: 373, 247, 221, 188, 160, 147, 127, 91, 65.

N-(4-chlorophenyl)-6-methyl-4-(2-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydropy-rimidine-5-carboxamide (4h)

IR (ν_{max} cm^{-1}, KBr): 3403 (N-H str.), 1702 (C=O str.) 1214 (C=S str.), 743 (C-Cl str.). ^{1}H NMR 400 Mz ($CDCl_3$+ DMSO d_6): 2.19 (s, 3H, -CH_3), 5.92 (s, 1H, Ha), 7.15–7.59 (m, 8H, Ar-H), 8.50 (s, 1H, -NH pyrimidine), 9.48 (s, 1H, -NH pyrimidine), 9.79 (s, 1H, -NH amide). EI^+ m/z: 393, 391, 356, 267, 265, 229, 206, 165, 143, 127, 101, 90, 67.

General Procedure of Synthesis of *N*-(4-chlorophenyl)-7-methyl-5-aryl-2,3-dihydro-5*H*-thiazolol[3,2-*a*]pyrimidine-6-carboxamide 5(a–h)

1,2-Dibromoethane (0.01 mol) was added to a boiling solution of 1,2,3,4-tetrahydropyrimidine-2-thiones (0.01 mol) in dimethyl formamide (5 ml) and then refluxed for 45 min. The resulting solution was allowed to stand at room temperature, and the precipitated mineral salts were isolated by filtered through a Buchner funnel. The residue was triturated with sodium bicarbonate solution followed by ethanol and purified by column chromatography (Silica gel, hexane/ethyl acetate 7:3) to give analytical grade pure products **5(a–h)**.

N-(4-chlorophenyl)-7-methyl-5-(3,4-dimethoxyphenyl)-2,3-dihydro-5H-thiazolol-[3,2-a]-pyrimidine-6-carboxamide (5a)

IR (ν_{max} cm^{-1}, KBr): 3420 (N-H str.), 1706 (C=O str.). 684 (C-S-C str.). ^{1}H NMR 400 Mz ($CDCl_3$+ DMSO d_6): 2.22 (s, 3H, -CH_3), 3.16–3.58 (m, 4H, CH_2-CH_2), 3.80 (s, 3H, -OCH3), 3.82 (s, 3H, -OCH3), 5.58 (s, 1H, Ar-Hc), 6.98–7.44 (m, 7H, Ar-H), 9.03 (S, 1H, NH-amide). EI^+ m/z: 443, 317, 413, 398, 287, 275, 244, 159, 153, 127, 115, 86.

N-(4-chlorophenyl)-7-methyl-5-(4-methoxyphenyl)-2,3-dihydro-5H-thiazolol[3,2-a]-pyrimidine-6-carboxamide (5b)

IR (ν_{max} cm^{-1}, KBr): 3378 (N-H str.), 1698 (C=O str.), 678 (C-S-C str.). ^{1}H NMR 400 Mz ($CDCl_3$+ DMSO d_6): 2.16 (s, 3H, -CH_3), 3.12–3.46 (m, 4H, CH_2-CH_2), 3.80 (s, 3H, -OCH3), 5.45 (s, 1H, Ar-Hc), 6.87–7.52 (m,

9H, Ar-H). EI^+ m/z: 413, 398, 287, 275, 259, 244, 185, 159, 153, 127, 115, 86, 67.

N-(4-chlorophenyl)-7-methyl-5-(2-methoxyphenyl)-2,3-dihydro-5H-thiazolol[3,2-a]-pyrimidine-6-carboxamide (5c)

IR (ν_{max} cm^{-1}, KBr): 3401 (N-H str.), 1707 (C=O str.), 680 (C-S-C str.). ^1H NMR 400 Mz ($CDCl_3$+ DMSO d_6): 2.31 (s, 3H, $-CH_3$), 3.08–3.26 (m, 4H, CH_2-CH_2), 3.85 (s, 3H, -OCH3), 5.96 (s, 1H, Ar-Hc), 6.90–7.47 (m, 9H, Ar-H). EI^+ m/z: 413, 398, 287, 259, 243, 181, 159, 153, 127, 115, 86, 67.

N-(4-chlorophenyl)-7-methyl-5-phenyl-2,3-dihydro-5H-thiazolol[3,2-]pyrimidine-6-carboxamide (5d)

IR (ν_{max} cm^{-1}, KBr): 3397 (N-H str.), 1710 (C=O str.), 682 (C-S-C str.). ^1H NMR 400 Mz ($CDCl_3$+ DMSO d_6): 2.14 (s, 3H, $-CH_3$), 3.18–3.67 (m, 4H, CH_2-CH_2), 5.60 (s, 1H, Ha), 7.06–7.52 (m, 9H, Ar-H), 9.03 (s, 1H, -NH amide). EI^+ m/z: 383, 368, 306, 257, 242, 179, 155, 127, 115, 86, 67.

N-(4-chlorophenyl)-7-methyl-5-(3-nitorphenyl)-2,3-dihydro-5H-thiazolol[3,2-a]-pyrimi-dine-6-carboxamide (5e)

IR (ν_{max} cm^{-1}, KBr): 3388 (N-H str.), 1704 (C=O str.), 680 (C-S-C str.). ^1H NMR 400 Mz ($CDCl_3$+ DMSO d_6): 2.24 (s, 3H, $-CH_3$), 3.22–3.47 (m, 4H, CH_2-CH_2), 5.71 (s, 1H, Ar-Hc), 7.21–8.23 (m, 9H, Ar-H). EI^+ m/z: 428, 399, 302, 275, 243, 228, 153, 127, 115, 86, 67.

N-(4-chlorophenyl)-7-methyl-5-(3-hydroxyphenyl)-2,3-dihydro-5H-thiazolol[3,2-a]-pyrimidine-6-carboxamide (5f)

IR (ν_{max} cm^{-1}, KBr): 3367 (N-H str.), 1677 (C=O str.), 687 (C-S-C str.). ^1H NMR 400 Mz ($CDCl_3$+ DMSO d_6): 2.20 (s, 3H, $-CH_3$), 3.18–3.66 (m, 4H, CH_2-CH_2), 5.53 (s, 1H, Ar-Hc), 6.67–7.56 (m, 8H, Ar-H), 9.43 (s, 1H, -OH amide), 9.49 (s, 1H, -NH amide). EI^+ m/z: 399, 384, 306, 273, 245, 171, 153, 127, 115, 86, 67.

N-(4-chlorophenyl)-7-methyl-5-(2-hydroxyphenyl)-2,3-dihydro-5H-thiazolol[3,2-a]-pyrimidine-6-carboxamide (5g)

IR (ν_{max} cm^{-1}, KBr): 3377 (N-H str.), 1688 (C=O str.), 685 (C-S-C str.). ^1H NMR 400 Mz ($CDCl_3$+ DMSO d_6): 2.26 (s, 3H, $-CH_3$), 3.19–3.63 (m, 4H, CH_2-CH_2), 4.88 (s, 1H, Ar-Hc), 6.87–7.65 (m, 8H, Ar-H), 10.29 (s, 1H, -OH amide), 10.32 (s, 1H, -NH amide). EI^+ m/z: 399, 385, 303, 272, 245, 171, 153, 127, 115, 86, 67.

N-(4-chlorophenyl)-7-methyl-5-(2-chlorophenyl)-2,3-dihydro-5H-thiazolol[3,2-a]-pyrim-idine-6-carboxamide (5h)

IR (ν_{max} cm^{-1}, KBr): 3398 (N-H str.), 1706 (C=O str.), 683 (C-S-C str.). ^{1}H NMR 400 Mz ($CDCl_3$+ DMSO d_6): 2.19 (s, 3H, -CH_3), 3.12–3.64 (m, 4H, CH_2-CH_2), 5.53 (s, 1H, Ar-Hc), 7.19–7.36 (m, 10H, Ar-H). EI^+ m/z: 417, 402, 291, 276, 263, 227, 189, 153, 127, 99, 86, 67.

REFERENCES

[1] R. Vitolina and A. Kimenis, *Khim.-Farm. Zh.,* **23,** 285 (1989).
[2] V. V. Kastron, R. Vitolina, E. L. Khanina, G. Duburs, A. Kimenis, N. V. Kondratenko, V. I. Popov, L. M. Yagupolskii, and A. A. Kolomeitsev, U.S. Patent, 4738965 (1988); *Chem. Abstr.,* **110,** 18547h (1989).
[3] H. Cho, M. Ueda, K. Shima, A. Mizuno, M. Hayashimatsu, Y. Ohnaka, Y. Takeuchi, M. Hamaguchi, K. Aisaka, T. Hidaka, M. Kawai, M. Takeda, T. Ishihara, K. Funahashi, F. Satoh, M. Morita, and T. Noguchi,*J. Med. Chem.,* **32,** 2399 (1989).
[4] G. C. Rovynak, K. S. Atwal, A. Hedberg, S. D. Kimball, S. Moreland, J. Z. Gougoutas, B. C. O'Reilly, J. Schwartz, and M. F. Malley, *J. Med. Chem.,* **35,** 3254 (1992).
[5] M. Ertan, A. Balkan, S. Sarac, S. Uma, J. F. Renaudand, and Y. Rolland, *Arch. Pharm., (Weinheim)*, **324,** 135 (1991).
[6] M. Ertan, A. Balkan, S. Sarac, S. Uma, K. Rubseman, and J. F. Renaud, *Arzneim.-Forsch.:Drug Res.*, **41,** 725 (1991).
[7] A. Balkan, M. Ertan, and T. Burgemeister, *Arch. Pharm., (Weinheim)* **325,** 499 (1992).
[8] A. Balkan, S. Uma, M. Ertan, and W. Wiegrebe, *Pharmazie,* **47,** 687 (1992).
[9] A. Balkan, B. Tozkoparan, M. Ertan, Y. Sara, and N. Ertekin, *Boll. Chim. Farm.,* **135,** 648 (1996).
[10] G. Doria, C. Passarotti, R. Sala, R. Magrini, P. Sberze, M. Tibolla, R. Ceserani, G. Arcari, R. Castello, and D. Toti, *Il Farmaco-Ed. Sc.,* **40,** 885 (1985).
[11] E. Jeanneau-Nicolle, M. Benoit-Guyod, A. Namil, and G. Leclerc, *Eur. J. Med. Chem.,* **27,** 115 (1992).
[12] B. Tozkoparan, M. Ertan, P. Kelicen, and R. Demirdamar, *Il Farmaco,* **54,** 588 (1999).
[13] J. Baetz (Seperic), British Patent, GB 1334628 (1973); *Chem. Abst.*, **80,** 48028u (1974).
[14] B. Dash, M. Patra, and P. K. Mohapatra, *J. Inst. Chem.,* **52,** 92 (1980); *Chem. Abstr.*, **93,** 239353z (1980).
[15] Teijin Ltd., Japanese Patent, *Jpn. Kokai Tokkyo Koho JP*, 58 24590 [83 24590] (1983).; *Chem. Abstr.,* **98,** 215611j (1983).
[16] D. Bigg (Synthelabo S.A.), French patent, *Fr. Demande FR,* 2479831 (1981); *Chem. Abstr.*, **96,** 162725z (1982).
[17] J. Mohan, V. K. Chadha, H. S. Chaudhary, B. D. Sharma, and H. K. Pujari, *Indian J. Exp. Biol.*, **10,** 37 (1972).
[18] S. N. Dehuri and A. Nayak, *J. Ind. Chem. Soc.,* **60,** 970 (1983).
[19] H. R. Champaneri, S. R. Modi, and H. B. Naik, Studies on pyrimidines. *Asian J. Chem.,* **6,** 737 (1994); *Chem. Abstr.* **121,** 300842y (1994).
[20] C. O Kappe and P. Roschger, *J. Heterocycl. Chem.,* **26,** 55 (1989).
[21] A. Balkan, M. Ertan, and T. Burgemeister. *Arch. Pharm.(Weinheim),* **325,** 499 (1992).

[22] (a) A. Mobinikhaledi, N. Foroughifar, and F. Goodarzi. *Phosphorus, Sulfur, and Silicon Relat. Elem.,* **179,** 507 (2004); (b) A. Mobinikhaledi, N. Foroughifar, and B. Ahmadi, *Phosphorus, Sulfur, and Silicon Relat. Elem.,* **180,** 339 (2005).
[23] (a) P. Biginelli, *Gazz. Chim. Ital*., **23,** 360 (1893); (b) C. O. Kappe and S. F. Falsone, *Synlett.,* 718 (1998), and references therein.
[24] A. Kocabalkanli, O. Ates, and G. Otuk, *Arch. Pharm. Pharm. Med. Chem.,* **334,** 35 (2001).