Advanced Pharmaceutical Bulletin, **2012**, 2(2), 213-222
doi: 10.5681/apb.2012.033
http://apb.tbzmed.ac.ir/

Synthesis and Pharmacological Evaluation of Some New Pyrimidine Derivatives Containing 1,2,4-Triazole

Shantaram Gajanan Khanage[1]*, S. Appala Raju[2], Popat Baban Mohite[3], Ramdas Bhanudas Pandhare[3]

[1] *Research scholar, Department of Pharmacy,Vinayaka Missions University, Salem, Sankari main road, NH-47,Tamilnadu, India.*

[2] *Department of Pharmaceutical chemistry, H.K.E.'S College of Pharmacy, Sedam road, Gulbarga, Karnataka, India.*

[3] *Department of Pharmaceutical chemistry, M.E.S. College of Pharmacy, Sonai, Tq-Newasa, Dist.-Ahmednagar, Maharashtra, India.*

ARTICLE INFO

Article Type:
Research Article

Article History:
Received: 15 July 2012
Accepted: 30 July 2012
ePublished: 15 Aug 2012

Keywords:
Chalcones
Condensation
Dihydropyrimidine
Antimicrobial activity
MES activity
Antitumor agent

ABSTRACT

Purpose: An efficient method has been described for synthesis of 6-(substituted aryl)-4-(3,5-diphenyl-1H-1,2,4-triazol-1-yl)-1, 6-dihydropyrimidine-2-thiol, as a beneficial antimicrobial, anticonvulsant and anticancer agents. ***Methods:*** The clalcones of title compounds were synthesized in three steps and subsequently these chalcones were further reacted with thiourea in the presence of KOH in ethanol, which led to the formation of dihydropyrimidine derivatives (4a-j). Compounds 4a-j were screened for their *in vitro* antimicrobial activity by agar well method and their anticonvulsant activity by the MES model. Anticancer activity of two newly synthesized heterocycles were evaluated at National Cancer Institute (NCI) Maryland, USA against 60 cell lines of different human tumor at a single dose of 10^{-5}M. ***Results:*** Compound 4b, 4c, 4d, 4i and 4j were exhibited significant antimicrobial potential against tested strains at 50µg/ml and 100µg/ml concentrations. Out of the ten compounds studied 4a, 4b, 4c, 4h and 4j showed comparable MES activity to Phenytoin and Carbamazepine after 0.5h. Tested compounds did not showed to be more potent than standard drugs after 4h. Compound 4a and 4d were found active on Non-Small Cell Lung Cancer (HOP-92). ***Conclusion:*** Ten noveldihydropyrimidine analogues has been synthesized, characterized and found to bepromising antibacterial, anticonvulsant and antitumor agents.

Introduction

Heterocycles bearing a symmetrical triazole moiety were reported to show a broad spectrum of pharmacological properties like anticancer,[1,2] antimicrobial,[3-6]anticonvulsant,[7] antiinflammatory, analgesic[8,9] antidepressant,[10] antitubercular,[11,12] antimalarial[13] and hypoglycemic[14] activities. The pyrimidine ring system is a six membered heterocyclic ring structure composed of two nitrogen atoms and used in the synthesis of pharmaceuticals. The pyrimidine moiety is a versatile lead molecule in pharmaceutical development and has a wide range of biological activities. In the past few years, the therapeutic interest of pyrimidine derivatives in pharmaceutical and medicinal field has been given a great attention to the medicinal chemist. Literature survey reveals that pyrimidine derivatives are well known to have antimicrobial,[15-17] antimalarial,[18] anticonvulsant,[19] anticancer,[20] antiinflammatory, analgesic,[21,22] antitubercular[23] activities. In recent years, the extensive studies have been focused on pyrimidine derivatives because of their diverse chemical reactivity, accessibility and wide range of biological activities. We have recently reported the *in vitro* antimicrobial potential of 1-(3,5-diphenyl-1H-1,2,4-triazol-1-yl)-3-(substituted aryl) prop-2-en-1-one (chalcones) and MIC values of different derivatives were determined by liquid broth method.[24]

The widespread properties of 1,2,4-triazoles and pyrimidines have prompted us to synthesize them in single molecular framework in order to study their pharmacological activity. Hence, the present investigation was undertaken to study the antimicrobial, anticonvulsant and antitumorpotential ofpyrimidine derivatives containing 1,2,4-triazole moiety. In this dissertation, we achieved the successful synthesis and significant antimicrobial, anticonvulsant and anticancer potential of a series of 6-(substituted aryl)-4-(3,5-diphenyl-1*H*-1,2,4-triazol-1-yl)-1,6-dihydropyrimidine-2-thiol (4a-j).

Materials and methods

The chemicals and solvents used for the experimental work were commercially procured from E. Merck India and Qualigens India. The melting points of all synthesized compounds were determined by open tube capillary using Thermonik precision apparatus in

***Corresponding author:** Shantaram Gajanan Khanage, M.E.S. College of Pharmacy, Sonai, At post-Sonai, Tq-Newasa, Dist.-Ahmednagar, Maharashtra-414105, India. Fax-02427 230948, Phone: +91 9822652921, Email: shantaram1982@gmail.com

Celsius scale and uncorrected. IR spectra were recorded using KBr pellets on PERKIN ELMER 8201 PC IR spectrophotometer, ^{1}H-NMR spectra of the final compounds 4a-j were recorded on BRUKER DRX NMR spectrometer (400 MHz). All spectra were obtained in DMSO. Mass spectra (FAB-MS) of compounds 4a-j were recorded on 70V on JEOL D-300 spectrophotometer (Jeol Ltd., Tokyo, Japan). Elemental analysis for C, H and N were performed on a PERKIN ELMER 240 elemental analyzer.

Synthesis protocol

Compounds 1, 2, and 3a-j were synthesized according to the reported method.[24]

Synthesis of 3,5-diphenyl-1H-1,2,4-triazole (1)

Benzohydrazide (0.1 mole) was dissolved in methanol, to this solution benzamide (0.1 mole) was added and stirred to get clear solution, then the resulting reaction mixture was refluxed for two hours on water bath. Therafter the reaction mixture was cooled at room temperature and poured in ice cold water to get precipitated 3,5-diphenyl-1*H*-1,2,4-triazole. Then obtained product was recrystallized by dioxane:ethanol mixture with an yield 83 %, m.p. 196-198°C.

Synthesis of 1-(3,5-diphenyl-1H-1, 2, 4-triazol-1-yl) ethanone (2)

To a solution of compound 1 (0.05 mole) dissolved in methanol, acetic anhydride (0.05 mole) and 2-3 drops of concentrated sulfuric acid were added, then the resulting reaction mixture was warmed on a water bath for 20 min. The reaction mixture was cooled at room temperature and poured in to ice cold water to get precipitate of compound 2. The precipitate of compound 2 was purified by dioxane:ethanol mixture with an yield 76 %, m.p. 176-178°C.

General procedure for synthesis of 1-(3,5-diphenyl-1H-1,2,4-triazol-1-yl)-3-(substituted aryl) prop-2-en-1-one(Chalcones) 3a-j

Compound 2 (0.05 mole) in methanol was treated with substituted aromatic aldehydes (0.05 mole) and 20% 10 ml NaOH, afterward stirred the reaction mixture for 7-8 hours at room temperature. The mixture was poured in ice cold water to get precipitate of compounds 3a-j, subsequently recrystallized by dioxane:ethanol mixture.

General procedure for synthesis of 6-(substituted aryl)-4-(3,5-diphenyl-1H-1,2,4-triazol-1-yl)-1,6-dihydropyrimidine-2-thiol (4a-j)

A mixture of 0.01 mole of the required chalcones (3a-j), 0.01 mole thiourea and KOH (1gm) in 20 ml ethanol was heated under reflux for 6 hours, then cooled and poured on to crushed ice. The solid product obtained was filtered and recrystallized from dioxane:ethanol mixture.

Physical and spectral data of the compounds 4a-j are mentioned bellow.

Physical and spectral data of compounds 4a-j.

***6-(4-chlorophenyl)-4-(3,5-diphenyl-1H-1,2,4-triazol-1-yl)-1,6-dihydropyrimidine-2-thiol* (4a).**

Yield 67 %, m.p. 120-122°C. Elemental analysisFound C 64.89; H 4.02; N 15.70, Calculated for ($C_{24}H_{18}ClN_5S$), C 64.93; H 4.09; N 15.78.IR(KBr, cm^{-1}): 2940, 3075, 3151 (Ar-CH), 1629 (C=N, triazole), 1415 (C=C, pyrimidine), 787 (-Cl), 2626 (-SH). MS m/z: 443(M^+). ^{1}H NMR (400 MHZ, DMSO) δ: 7.69-8.40 (14H, m, Ar-H), 4.46 (d, 1H, NH-C<u>H</u>), 5.92 (d, 1H, CH), 13.39 (S, 1H, Ar-SH), 5.27 (s, 1H, NH).

***6-(2-chlorophenyl)-4-(3,5-diphenyl-1H-1,2,4-triazol-1-yl)-1,6-dihydropyrimidine-2-thiol*(4b).**

Yield 71 %, m.p. 125-127°C. Elemental analysisFound C 64.84; H 4.12; N 15.72, Calculated for ($C_{24}H_{18}ClN_5S$), C 64.93; H 4.09; N 15.78.IR(KBr, cm^{-1}): 2939, 3073, 3175 (Ar-CH), 1624 (C=N, triazole), 1419 (C=C, pyrimidine), 779 (-Cl), 2616 (-SH). MS m/z: 443(M^+). ^{1}H NMR (400 MHZ, DMSO) δ: 7.65-8.47(14H, m, Ar-H), 4.48 (d, 1H, NH-C<u>H</u>), 5.94 (d, 1H, CH), 13.41 (S, 1H, Ar-SH), 5.25 (s, 1H, NH).

***6-(3-nitrophenyl)-4-(3,5-diphenyl-1H-1,2,4-triazol-1-yl)-1,6-dihydropyrimidine-2-thiol*(4c).**

Yield 65 %, m.p. 107-109°C. Elemental analysisFound C 63.44; H 4.06; N 18.40, Calculated for ($C_{24}H_{18}N_6O_2S$), C 63.42; H 3.99; N 18.49.IR(KBr, cm^{-1}): 2942, 3078, 3180 (Ar-CH), 1628 (C=N, triazole), 1417 (C=C, pyrimidine), 1551 (-NO_2), 2619 (-SH). MS m/z: 454(M^+). ^{1}H NMR (400 MHZ, DMSO) δ: 7.64-8.38 (14H, m, Ar-H), 4.45 (d, 1H, NH-C<u>H</u>), 5.96 (d, 1H, CH), 13.44 (S, 1H, Ar-SH), 5.26 (s, 1H, NH).

***6-(4-methoxyphenyl)-4-(3,5-diphenyl-1H-1,2,4-triazol-1-yl)-1,6-dihydropyrimidine-2-thiol*(4d).**

Yield 68 %, m.p. 130-132°C. Elemental analysisFound C 68.33; H 4.82; N 15.83, Calculated for ($C_{25}H_{21}N_5OS$), C 68.32; H 4.82; N 15.93.IR(KBr, cm^{-1}): 2947, 3075, 3181 (Ar-CH), 1625 (C=N, triazole), 1415 (C=C, pyrimidine), 1159 (-OCH_3), 2618 (-SH). MS m/z: 439(M^+). ^{1}H NMR (400 MHZ, DMSO) δ: 7.64-8.38 (14H, m, Ar-H), 4.44(d, 1H, NH-C<u>H</u>), 5.96 (d, 1H, CH), 13.55 (S, 1H, Ar-SH), 3.82 (3H, s, OCH_3),5.27 (s, 1H, NH).

***6-(4-dimethylaminophenyl)-4-(3,5-diphenyl-1H-1,2,4-triazol-1-yl)-1,6-dihydropyrimidine-2-thiol*(4e).**

Yield 74 %, m.p. 140-142°C. Elemental analysisFound C 69.06; H 5.33; N 18.57, Calculated for ($C_{26}H_{24}N_6S$), C 69.00; H 5.35; N 18.57.IR(KBr, cm^{-1}): 2939, 3076, 3174 (Ar-CH), 1623 (C=N, triazole), 1412 (C=C, pyrimidine), 3159, 3146 (-NCH_3), 2606 (-SH). MS m/z: 452(M^+). ^{1}H NMR (400 MHZ, DMSO) δ: 7.61-8. 56 (14H, m, Ar-H), 4.47(d, 1H, NH-C<u>H</u>), 5.90 (d, 1H, CH), 13.49 (S, 1H, Ar-SH), 3.19 (6H, s, -N(CH_3)2), 5.23 (s, 1H, NH).

***6-(phenyl)-4-(3,5-diphenyl-1H-1,2,4-triazol-1-yl)-1,6-dihydropyrimidine-2-thiol* (4f).**
Yield 72 %, m.p. 115-117°C. Elemental analysisFound C 70.36; H 4.60; N 17.19, Calculated for ($C_{24}H_{19}N_5S$), C 70.39; H 4.68; N 17.10.IR(KBr, cm^{-1}): 2946, 3072, 3182 (Ar-CH), 1621 (C=N, triazole), 1411 (C=C, pyrimidine), 2609 (-SH). MS m/z: 409(M^+). ^{1}H NMR (400 MHZ, DMSO) δ: 7.56-8.39 (15H, m, Ar-H), 4.45 (d, 1H, NH-CH), 5.93 (d, 1H, CH), 13.61 (S, 1H, Ar-SH), 5.29 (s, 1H, NH).

***6-(2-furul)-4-(3,5-diphenyl-1H-1,2,4-triazol-1-yl)-1,6-dihydropyrimidine-2-thiol*(4g).**
Yield 68 %, m.p. 111-123°C. Elemental analysisFoundC 66.12; H 4.34; N 17.44, Calculated for ($C_{22}H_{17}N_5OS$), C 66.15; H 4.29; N 17.53.IR(KBr, cm^{-1}): 2942, 3079, 3178 (Ar-CH), 1628 (C=N, triazole), 1416 (C=C, pyrimidine), 1224 (C-O-C), 2611 (-SH). MS m/z: 399(M^+). ^{1}H NMR (400 MHZ, DMSO) δ: 7.06-8. 37 (13H, m, Ar-H), 4.46 (d, 1H, NH-CH), 5.97(d, 1H, CH), 13.47 (S, 1H, Ar-SH), 5.28 (s, 1H, NH).

***6-(4-bromophenyl)-4-(3,5-diphenyl-1H-1,2,4-triazol-1-yl)-1,6-dihydropyrimidine-2-thiol*(4h).**
Yield 58 %, m.p. 117-119°C. Elemental analysisFound C 59.04; H 3.67; N 14.39, Calculated for ($C_{24}H_{18}BrN_5S$), C 59.02; H 3.71; N 14.34.IR(KBr, cm^{-1}): 2936, 3066, 3173 (Ar-CH), 1625 (C=N, triazole), 1413 (C=C, pyrimidine), 698 (-Br), 2615 (-SH). MS m/z: 488(M^+). ^{1}H NMR (400 MHZ, DMSO) δ: 7.55-8.48 (14H, m, Ar-H), 4.47 (d, 1H, NH-CH), 5.94 (d, 1H, CH), 13.38 (S, 1H, Ar-SH), 5.27 (s, 1H, NH).

***6-(4-hydroxyphenyl)-4-(3,5-diphenyl-1H-1,2,4-triazol-1-yl)-1,6-dihydropyrimidine-2-thiol*(4i).**
Yield 72 %, m.p. 127-129°C. Elemental analysisFoundC 67.79; H 4.49; N 16.42, Calculated for ($C_{24}H_{19}N_5OS$), C 67.74; H 4.50; N 16.46.IR(KBr, cm^{-1}): 2946, 3073, 3175 (Ar-CH), 1622 (C=N, triazole), 1412 (C=C, pyrimidine), 3357 (-OH), 2616 (-SH). MS m/z: 425(M^+). ^{1}H NMR (400 MHZ, DMSO) δ: 7.48-8.59 (14H, m, Ar-H), 4.49 (d, 1H, NH-CH), 5.96 (d, 1H, CH), 13.41 (S, 1H, Ar-SH), 10.16 (s, 1H, Ar-OH), 5.26 (s, 1H, NH).

***6-(2,4-dimethoxyphenyl)-4-(3,5-diphenyl-1H-1,2,4-triazol-1-yl)-1,6-dihydropyrimidine-2-thiol*(4j).**
Yield 65 %, m.p. 133-135°C. Elemental analysisFound C 66.59; H 4.89; N 14.92, Calculated for ($C_{26}H_{23}N_5O_2S$), C 66.50; H 4.94; N 14.91.IR(KBr, cm^{-1}): 2941, 3079, 3186 (Ar-CH), 1624 (C=N, triazole), 1416 (C=C, pyrimidine) 1155 (-OCH_3), 2626 (-SH). MS m/z: 469(M^+). ^{1}H NMR (400 MHZ, DMSO) δ: 7.31-8.44 (13H, m, Ar-H), 4.45 (d, 1H, NH-CH), 5.95 (d, 1H, CH), 13.39 (S, 1H, Ar-SH), 3.89 (6H, s, OCH_3), 5.28 (s, 1H, NH).

Pharmacological assessment

Antimicrobial Activity

The *in vitro* antimicrobial activity of the target compounds 4a-j was performed by agar well method (diffusion technique) against *S. aureus* NCIM 2079, *E. coli* NCIM 2065, *C. albicans* NCIM 3471 and *A. niger* NCIM 1196. The antibiotic Ampicillin and the antifungal agent Fluconazole were used as standard drugs for the study. The fresh bacterial culture was obtained by inoculating bacteria into peptone water liquid media and incubating at 37± 2 °C for 18-24 hours. This culture was mixed with nutrient agar media and poured in to Petri dishes. After culture media solidification four wells were made at equal distance by using a sterile steel cork borer (8mm diameter). In to these wells different concentrations of standard drug and synthesized compounds were introduced. Dimethyl Formamide (DMF) was used as a control. After introduction of standard drug and synthesized compounds, the plates were placed in a refrigerator at 8-10 °C for proper diffusion of drugs into the media. After two hours of cold incubation, the Petri plates were transferred to incubator and maintained at 37±2 °C for 18-24 hours. After the incubation period, the petri plates were observed for growth inhibition zone by using vernier scale. The results were evaluated by comparing the growth inhibition zone shown by the synthesized compounds with standard drugs. The results were presented as the mean value of growth inhibition zone measured in millimeters of three sets (Table 1). The standard drugs and synthesized compounds were dissolved in a minimum quantity of Dimethyl Formamide (DMF) and adjusted, to made up the volume with distilled water to get 50µg/ml and 100µg/ml concentrations.

Anticonvulsant Activity: Maximal Electroshock Seizure Test (MES)

The compounds 4a-j were screened for their anticonvulsant activity by Maximal electroshock seizure method. Study protocol was approved by the Institutional Animal Ethics Committee for the purpose of control and supervision on experiments on animals (IAEC, Approval No.1211/ac/08/CPCSEA) before experiment. Initial anticonvulsant evaluations of the test compounds were undertaken by following the anticonvulsant drug development (ADD) program protocol.[25] The animals Albino mice (20-25 g) of either sex were stimulated through corneal electrodes to 50 mA current at a pulse of 60 Hz applied for 0.2 s. Animals were previously given the test drug intraperitoneally. Abolition of the hind limb tonic extension spasm was recorded as the anticonvulsant activity. The test compounds were suspended in a 0.5% methyl cellulose-water mixture. In preliminary screening, each compound was administered through an intraperitoneally injection at three dose levels (30, 100 and 300 mg/kg) and the anticonvulsant activity was assessed after 0.5 h and 4 h intervals of administration. The anticonvulsant efficacy was evaluated by the maximal electroshock-induced seizure (MES) and screening data of compounds 4a-j are presented in Table 2.

Table 1. Antimicrobial activity of compounds 4a-j.

Compound	Zone of inhibition (in mm)							
	S. aureus		*E. coli*		*C. albicans*		*A. niger*	
	50µg	100µg	50µg	100µg	50 µg	100µg	50 µg	100µg
4a	19	21	18	23	20	23	18	21
4b	18	21	19	23	22	25	23	22
4c	21	24	24	24	19	22	18	23
4d	19	22	19	22	23	22	22	21
4e	18	19	17	20	20	21	19	20
4f	15	17	14	17	18	19	16	18
4g	16	19	17	20	15	19	17	21
4h	19	21	21	19	19	22	21	19
4i	21	19	22	20	21	18	22	22
4j	22	21	20	20	19	18	16	19
Ampicillin	21	25	24	26	-	-	-	-
Fluconazole	-	-	-	-	24	26	23	25
DMF	-	-	-	-	-	-	-	-

Table 2. Anticonvulsant and neurotoxicity screening of compounds 4a-j.

Sr. No.	Treatment	Ar	MES screen[a]		Neurotoxicity screen[a]	
			0.5h	4h	0.5h	4h
1	4a	4-Cl	30	300	300	_
2	4b	2-Cl	30	300	_	300
3	4c	3-NO_2	30	300	_	_
4	4d	4-OCH_3	100	300	300	300
5	4e	4-N(CH_3)2	100	300	_	300
6	4f	phenyl	100	300	300	300
7	4g	2-Furyl	100	300	_	_
8	4h	4-Br	30	300	300	300
9	4i	4-OH	100	300	_	300
10	4j	2,4-OCH_3	30	300	_	_
11	Phenytoin	_	30	30	100	100
12	Carbamazepine	_	30	100	300	300

"a" Doses of 30, 100 and 300 mg/kg were administered. The figures in the Table indicate the minimum dose whereby bioactivity was demonstrated in half or more of mice. The animals were examined 0.5 and 4 h after injections were given. The dash "-" indicates an absence of activity at maximum dose administered (300 mg/kg).

Neurotoxicity screening (NT)

The minimal motor impairment was measured in mice by the rotorod test.[26] The Albino mice (20-25 g) were trained to stay on an accelerating rotorod that rotated at 10 rotations/min and its diameter was 3.2 cm. Only those mice were taken for the test which could stay on the revolving rod for at least one minute. Trained animals were injected intraperitoneallywith the test

compounds at doses of 300 mg/kg. Neurotoxicity was indicated by the inability of the animal to maintain equilibration on the rod for at least for one minute.

Anticancer activity

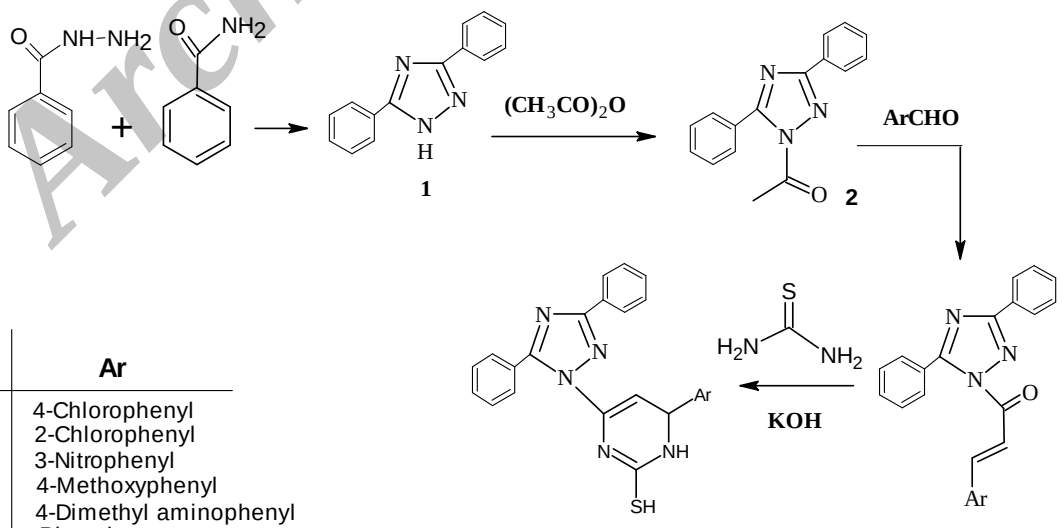
Anticancer activity of newly synthesized heterocycles were evaluated. Primarily compounds submitted at National Cancer Institute (NCI) Maryland, USA andselected compounds were screened for anticancer activity against 60 cell lines of different human tumor, representing leukemia, melanoma and cancers of the lung, colon, brain, ovary, breast, prostate, and kidney for one dose against the 60 cell lines at a single dose of 10^{-5}M. The mean growth %, range of growth % and growth % relative to most sensitive cell line is depicted in Table 3.

Results and discussion

The synthesis of 6-(substituted aryl)-4-(3,5-diphenyl-1*H*-1,2,4-triazol-1-yl)-1,6-dihydropyrimidine-2-thiol derivatives (4a-j)depicted in Figure 1. The compound1-(3,5-diphenyl-1*H*-1,2,4-triazol-1-yl)ethanone (2) on condensation with various aromatic aldehydes in NaOH solution yielded the corresponding chalcones (3a-j). These chalcones were further reacted with thiourea in the presence of KOH in ethanol, which led to the formation of dihydropyrimidine derivatives (4a-j) (Figure 2). The structural assessments of compounds 4a-j were carried out by IR, ^{1}H-NMR, Mass spectra and elemental analysis.Structures of compounds 4a-j were confirmed IR, ^{1}H-NMR, mass spectra and elemental analysis. Infrared spectrum of compounds 4a-j showed a sharp absorption band frequencies for-NO_2, -Cl, -OCH_3, -N-$(CH_3)_2$, -OH and -Br groups. Compounds 4a-j showed appropriate ^{1}H-NMR signals for aromatic protons and multiplets were observed in the range of δ 7.06-8.59. The ^{1}H NMR spectra showed a downfield singlet at around 13.4 ppm attributed to SH group. Mass spectraof the compounds 4a-j showed molecular ion peaks with high abundance at m/z in agreement with their molecular formula. Compounds 4a-j evaluated for their *in vitro* antimicrobial, anticonvulsant and anticancer activity.

Table 3. Anticancer screening data of selected compounds.

Compound No.	60 Cell lines in assay in 1-dose 10^{-5} M concentration			
(NSC code)	Mean growth (%)	Range growth (%)	Most sensitive cell line	Growth of most sensitive cell line (%)
4a (764753/1)	106.85	-27.71-55.23	Non-Small Cell Lung Cancer (HOP 92)	- 27.71
4d (764754/1)	103.26	-19.05-50.25	Non-Small Cell Lung Cancer (HOP 92)	-19.05



	Ar
3a and 4a	4-Chlorophenyl
3b and 4b	2-Chlorophenyl
3c and 4c	3-Nitrophenyl
3d and 4d	4-Methoxyphenyl
3e and 4e	4-Dimethyl aminophenyl
3f and 4f	Phenyl
3g and 4g	2-Furyl
3h and 4h	4-Bromophenyl
3i and 4i	4-Hydroxyphenyl
3j and 4j	2, 4 -Dimethoxyphenyl

Figure 1. Synthesis of compounds 4a-j.

The *in vitro* antimicrobial activity of tested compounds was determined by agar well method. The results are summarized in Table 1. These antimicrobial data clearly indicated that the presence of methoxy, chloro, nitro and hydroxysubstitution on phenyl ring of the pyrimidine nucleus produced remarkable improvement in antimicrobial activity. Phenyl substitution is weakly active among the synthesized compounds. Compound 4c showed significant antibacterial activity against *S. aureus* and *E. coli*. Compound 4b showed fungicidal potential against *C. albicans* and *A. niger*. The *in vitro* antimicrobial study clearly reveals that pyrimidine derivatives (4a-j) were found to be significant antimicrobial agents probably due to pharmacologically active pyrimidine nucleus attached with 1,2,4-triazole.

The target compounds (4a-j) were tested for anticonvulsant activity by maximal electroshock induced seizure (MES) test. The anticonvulsant and neurotoxicity data of the compounds and standard drugs are presented in Table 2. The compounds that exhibited the most potent anti-MES activity included 4a, 4b, 4c, 4h and 4j which have activity comparablewith Phenytoin and Carbamazepine.Minimal motor impairment was measured by the rotorod test. Compounds 4c, 4g,and4j successfully passed the rotorod test without any sign of neurological deficit, whereas compounds 4d, 4f and 4hexhibited neurologicaldeficit at the dose of 300 mg/kg *i.p.* Compounds with the electron withdrawing chloro substituent at the *ortho*and*para*position and bromo at *para* position on the phenyl ring of pyrimidine nucleus led to considerable increase in the activity but were relatively toxic. The presence of a bulkier electron donating methoxy group at *para*and*ortho*position on the phenyl ring of pyrimidine nucleus results increase in anticonvulsant activity. This may be due to the increase in lipophilicity of the compound. The nitro substituent at the *meta*position of the phenyl ring found to be equally active with chloro substitution but without sign of neurotoxity. The effect of the hydroxy, phenyl and furyl substitution were found to be less active compounds as compared to other tested compounds.

The compounds 4a and 4d were evaluated at single concentration of 10^{-5} M towards the panel of approximately 60 cancer cell lines derived from nine different cancer types. The mean growth %, range of growth % and growth % relative to most sensitive cell line is depicted in Table 3. The tested compounds showed a broad spectrum of growth inhibitory activity against human tumor cells, as well as some distinctive pattern of selectivity (Figure 3 and Figure 4). Compound 4a was found to be a highly active growth inhibitor of the Non-Small Cell Lung Cancer (HOP-92) and CNS Cancer cell line (SNB-75) with a growth % of most sensitive cell line to be - 27.71, whilst least active over other cell lines. The mean growth % for compound 4a was observed 106.85% and fall in a range - 27.71-55.23. Compound 4d showed selective antitumor sensitivity on Non-Small Cell Lung Cancer (HOP-92) and renal Cancer cell line (A498) with a growth % of most sensitive cell line to be -19.05, whilst least active over other cell lines. The mean growth % for compound 4d was observed 103.26% and fall in a range -19.05-50.25.

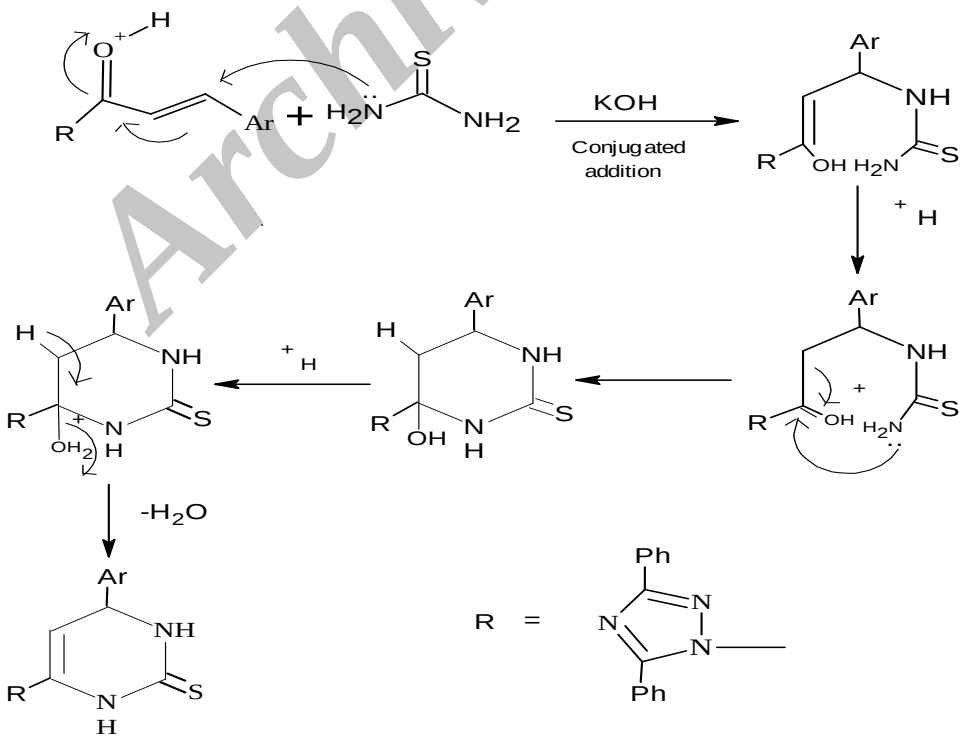


Figure 2. The possible mechanism involved in the formation of dihydropyrimidine derivatives (4a-j)from the respective chalcones is shown above.

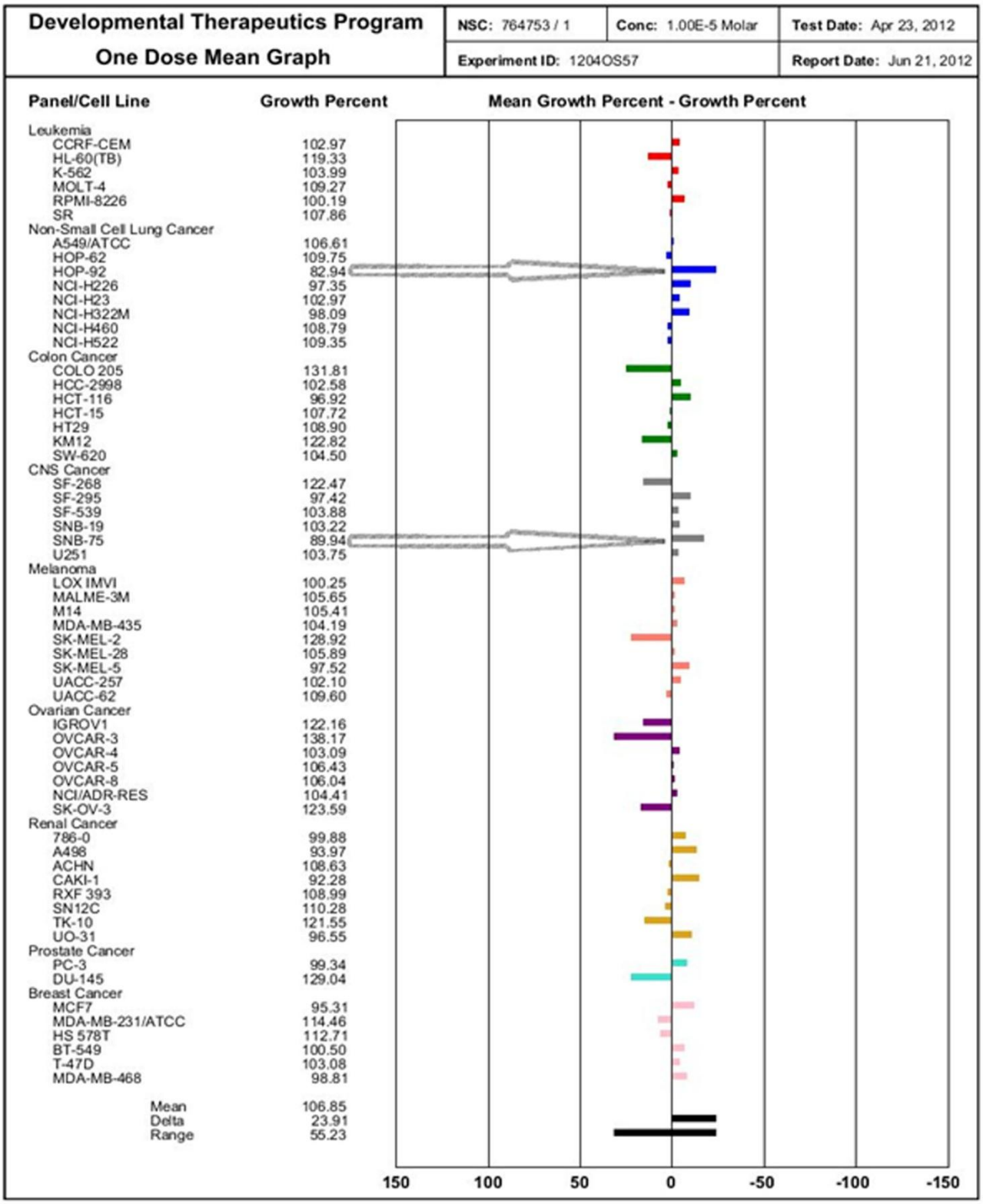


Figure 3. Selected NCI sixty cell screening data highlighting the potency of compound (4a: NSC: 764753/1) againstnon-Small Cell Lung Cancer (HOP-92) and CNS Cancer cell line (SNB-75). Bars to the right of the mean line represent cell lines more sensitive to test compound compared to mean, whereas bars to the left represent less sensitive cell lines.

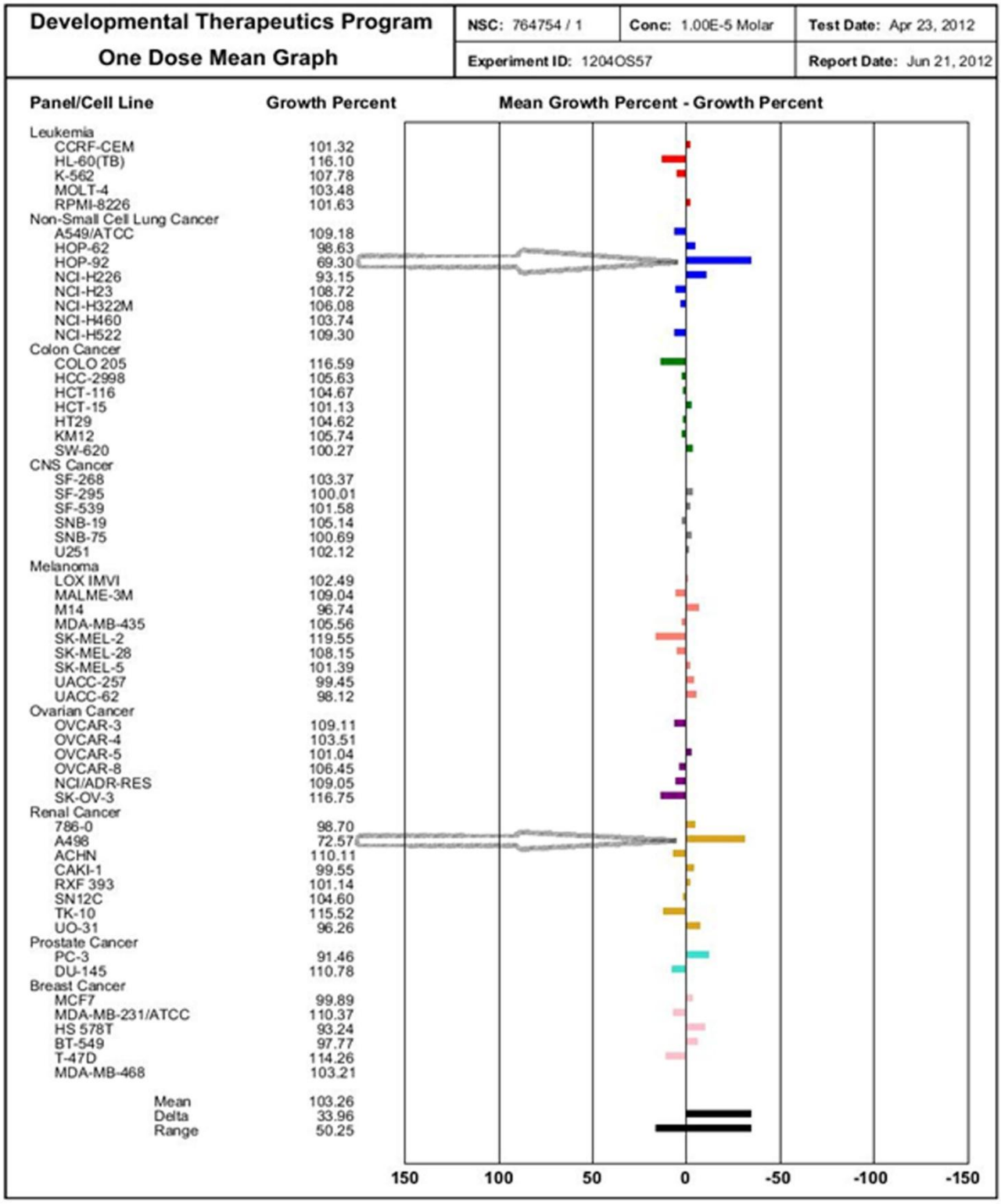


Figure 4. Selected NCI sixty cell screening data highlighting the potency of compound (4d: NSC: 764754/1) againstnon-Small Cell Lung Cancer (HOP-92) and renal Cancer cell line (A498). Bars to the right of the mean line represent cell lines more sensitive to test compound compared to mean, whereas bars to the left represent less sensitive cell lines.

Conclusion

In conclusion, new class of pyrimidine derivatives containing 1,2,4-triazole was synthesized and evaluated as antimicrobial, anticonvulsant and anticancer properties. The newly synthesized heterocycles exhibited promising antimicrobial activity against tested microorganisms. Compounds 4b, 4c, 4d, 4i and 4j were found to be the most active antimicrobial

agents from synthesized series. From the anticonvulsant screening data it was found that of 6-(substituted aryl)-4-(3,5-diphenyl-1H-1,2,4-triazol-1-yl)-1,6-dihydropyrimidine-2-thiol derivatives (4a-j) have encouraging anticonvulsant activity in the MES screen. Compound 4a, 4b, 4c, 4h and 4j found to be effective anticonvulsant agent from tested compounds. In the present study two compounds (4a and 4d) were tested for anticancer activity and most of them displayed antitumor activity on cell lines of Non-Small Cell Lung Cancer, CNS Cancer and renal Cancer.These results suggest that novel triazolechalcones and pyrimidine derivatives are interesting lead molecules for further synthetic and biological evaluation.

Acknowledgments
We are highly thankful to IICT Hyderabad for providing spectral data, NCL Pune for providing micro organisms for this study, National Cancer Institute (NCI) Bethesda, USA for *in vitro* screening of our compounds in human cancer cell lines. We are also grateful of Principal M.E.S. College Pharmacy, Sonai and PrashantPatilGadakh, Secreatary, Mula Education Society for providing excellent research facilities for this work.

Conflict of interest
The authors report no conflicts of interest.

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