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Synthesis And Anti-Cancer Activities Of Novel Pyrimidine -2-Thione Derivatives From Benzosuberones.

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ABSTRACT

A series of pyrimidine-2-thione derivatives were newly synthesized starting from 2, 3-dimethyl 6, 7, 8, 9-tetrahydro-5-H-benzo cyclohepten-5-one **1**. The anti tumor activity of the synthesized compounds was evaluated against 5 human tumor cell lines. Some of the tested compounds are shown better anti cancer activity against HeLa (human tumor cell). Additionally some more compounds are showing good to moderate activity against MCF7 (human breast adenocarcinoma cell lines).

Keywords: Benzosuberones, Arylidene derivatives, Pyrimidine -2- thiones, Anti cancer activity.

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INTRODUCTION

The pharmacological and anti tumor activities of many compounds containing heterocyclic rings have been reviewed. [1-7] In view of these reports and in continuation of our earlier work on heterocyclic systems [8-13] we have here in synthesized some new derivatives containing heterocyclic ring fused with substituted benzosuberones structure and evaluated for their anticancer activity. The structure of pyrimidines has been characterized by spectral analysis.Among these Compounds, **4e, 4g, 4h, 4i, 4j**, and **4k** are showing good to moderate anti cancer activity.

MATERIALS AND METHODS USED IN BIOLOGICAL ACTIVITIES

Five cell lines viz., HeLa: Homo sapiens cervix adenocarcinoma, B16-F10: Mouse skin melanoma (ATCC® CRL 6475™), SKOV3: Human Ovarian cancer (ATCC® HTB 77™), MCF7: Human Breast Adenocarcinoma (ATCC® HTB-22™), CHO-K1: Chinese hamster ovary cells, Normal Cell line (ATCC® CCL-61™) were obtained from the ATCC (Bethesda, MD, USA) and maintained in DMEM supplemented with 10 % FBS, 2 mM l-glutamine, 100 U/ml penicillin, and 100 µg/ml streptomycin at 37 °C in a 5 % CO_2 incubator. After seeding of cells in 96 well culture plate, allowed to attach properly.

Different concentrations of test compounds ranging from 1 to 50 µM were added in triplicates and incubated for 24hr. The cells were then incubated with MTT (0.5 mg/ml) for 3hr and to dissolve the insoluble formazan crystals 100 µl DMSO was added to each well. The absorbance of the plates was measured using a Synergy H1 multi-mode plate reader, USA. Doxorubicin and Mitomycin C were used as positive control for cancer cell lines and normal cell line respectively for comparison.

EXPERIMENTAL

Melting points were determined using Gallankamp apparatus and are Uncorrected. IR spectra were recorded on a FT – IR 1605 Perken Elmer; ^{1}H NMR in $CDCl_3$ on AVANCE 300 MHZ NMR spectrometer with TMS as an internal standard; and mass spectra on a VG – micro mass 7070 H mass spectrometer. TLC was run on silica gel G coated plates and iodine vapor as visualizing agent.

General Procedure for the synthesis of 2, 3 di-methyl 6-arylidene-6, 7, 8, 9-tetra hydro-5H-benzo [a] cyclohepten-5-ones [10] 3 (a-k): A mixture of 1(1.0 mmol), benzaldehyde (1.0 mmol)(2a) in ethanolic potassium hydroxide (1 g KOH in 10 ml of absolute ethanol) was stirred at room temperature for 0.5 hr.After completion of the reaction (TLC), the reaction mixture was neutralized with acetic acid and diluted with water. The solid thus obtained was filtered and washed thoroughly with water and dried. Recrystallized from methanol to give the product 3a.

(E)-6-(4-phenylarylidene)-2,3-dimethyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (3a): Yield 96%, colorless crystals; m.p. 124-126 ^{0}C; IR (KBr, cm^{-1}): 1662 (CO) 1616 (C=C); ^{1}H NMR ($CDCl_3$), 2.00-2.20 (m, 2H, 8-CH_2), 2.40 (s, 6H, 2CH_3), 2.70 (t, 2H, 7-CH_2), 2.85 (t, 2H, 9-CH_2), 7.00-7.75 (m, 8H, ArH) and 7.80 (s, 1H, C=CH). Anal. Calcd for $C_{20}H_{20}O$ requires C, 86.95; H, 7.26; O, 5.79%. Found: C, 86.88; H, 7.15; O, 5.77.
Remaining arylidene derivatives **3 (b-k)** are also prepared and analyzed in a similar manner.

Synthesisof9,10-dimethyl,3,4,6,7-tetrahydro-1H-benzo[6,7]cyclohepta[1,2-d]pyrimidine-2(5H)-thiones:-(**4a-k**): A mixture of compounds 3a (0.1 mmol) and thio urea (0.1 mmol) in ethanolic potassium hydroxide (0.4 g KOH in 20 ml of absolute ethanol) was refluxed for 4h. The reaction mixture was poured into ice cold water and then neutralized with hydrochloric acid (1N) and the compound obtained was filtered off, washed with water, dried and crystallized from appropriate solvent to give **4a**. Other compounds (**4a-k**) were prepared similarly and confirmed by spectral analysis.

9,10-dimethyl-4-phenyl-3,4,6,7-tetrahydro-1H-benzo[6,7]cyclohepta[1,2-d]pyrimidine-2(5H)-thione(4a): Yield 78%; m.p. 76-77 ^{0}C; IR (KBr, cm^{-1}): 3387, 3194 (2NH), 1197 (C=S); ^{1}H NMR ($CDCl_3$): δ 6.90-7.40 (m, 5H, Ar-H), 6.99 (s, 1H, Ar-H),6.90 (s, 1H, Ar-H), 5.10 (s, 1H, Pyrimidine-H), 2.85 (t, 2H, 6- CH_2), 2.30 (s, 6H, 8,9-di-CH_3), 2.00 (t, 2H, -4CH_2); 1.80 (q, 2H, 5 CH2); MS, m/z (%): 334.15(100). Anal. Calcd for C_{21} $H_{22}N_2S$: C, 75.41; H, 6.63; N, 8.38; S, 9.59. Found: C, 75.39; H, 6.62; N, 8.37; S, 9.58%;

-(4-bromophenyl)-9,10-dimethyl--3,4,6,7-tetrahydro-1H-benzo[6,7]cyclohepta[1,2-d]pyrimidine-2(5H)-thione (4b): Yield 88%; m.p. 74-75 ^{0}C; MS, m/z (%): 413(100). IR (KBr, cm^{-1}): 3414, 2929 (2NH), 1195 (C=S); ^{1}H NMR ($CDCl_3$): δ 7.60 (d, 2H, Ar-H), 7.40 (d, 2H, Ar-H), 6.99 (s, 1H, Ar-H),6.90 (s, 1H, Ar-H), 5.10 (s, 1H, Pyrimidine-H), 2.50 (t, 2H, 4- CH_2), 2.34 (s, 6H, 8,9-di-CH_3), 2.00 (t, 2H, -6CH_2), 1.90 (q, 2H, 5 CH2). Anal. Calcd for $C_{21}H_{21}BrN_2S$: C, 61.02; H, 5.12; Br, 19.33; N, 6.78; S, 7.76. Found: C, 61.00; H, 5.11; Br, 19.32; N, 6.77; S, 7.75%;

9,10-dimethyl-4-(p-tolyl)-3,4,6,7-tetrahydro-1H-benzo[6,7]cyclohepta[1,2-d]pyrimidine-2(5H)-thione(4c): Yield 81%; m.p. 124-25 ^{0}C; MS,m/z (%): 348(100). IR (KBr, cm^{-1}): 3392, 3198 (2NH), 1199 (C=S); ^{1}H NMR ($CDCl_3$), δ 7.25 (s, 4H, Ar-H), 6.99 (s, 1H, Ar-H), 6.90 (s, 1H, Ar-H), 5.0 (s, 1H, Pyrimidine-H), 2.80 (t, 2H, 6-CH_2), 2.60 (t, 2H, -4CH_2); 2.34 (s, 9H, 8,9-di-CH_3 &Ar-CH_3), 2.0 (q, 2H, 5 CH2). Anal. Calcd for $C_{22}H_{24}N_2S$; C, 75.82; H, 6.94; N, 8.04; S, 9.20. Found: C, 75.80; H, 6.92; N, 8.03; S, 9.19%.

4-(4-methoxyphenyl)9,10-dimethyl-3,4,6,7-tetrahydro-1H-benzo[6,7]cyclohepta[1,2-d]pyrimidine-2(5H)-thione(4d): Yield 72%; m.p. 84-85 ^{0}C; MS, m/z (%): 364(100). IR (KBr, cm^{-1}): 3394, 3196 (2NH), 1195 (C=S); ^{1}H NMR ($CDCl_3$), δ 6.99 (s, 1H, Ar-H), 6.90 (s, 1H, Ar-H), 6.87 (d, 2H, Ar-H), 5.10 (s, 1H, Pyrimidine-H), 3.80(s,1H, -OCH_3) , 2.85 (t, 2H, 6- CH_2), 2.34 (s, 6H, 8,9-di-CH_3), 2.00 (t, 2H, -4CH_2), 1.80 (q, 2H, 5 CH2). Anal. Calcd for $C_{22}H_{24}N_2OS$: C, 72.49; H, 6.64; N, 7.69; O, 4.39; S, 8.80. Found: C, 72.48; H, 6.63; N, 7.68; O, 4.38; S, 8.79%;

4(furan-2-yl)-9,10-dimethyl--3,4,6,7-tetrahydro-1H-benzo[6,7]cyclohepta[1,2-d]pyrimidine-2(5H)-thione(4e): Yield 78%; m.p. 120-21^{0}C; MS, m/z (%): 324(100). IR (KBr, cm^{-1}): 3388, 3197 (2NH), 1197 (C=S); ^{1}H NMR ($CDCl_3$), δ 7.60 (s, H, Furan-H), 7.40 (d, H, Furan -H), 6.99 (s, H, Ar-H), 6.90 (s, H, Ar-H),6.40 (d, 1H, Furan-H), 5.20 (s, 1H, Pyrimidine-H), 2.85 (t, 2H, 6- CH_2), 2.34 (s, 6H, 8,9-di-CH_3), 2.00 (t, 2H, -4CH_2); 1.80 (q, 2H, 5 CH2). Anal. Calcd for $C_{19}H_{20}N_2OS$: C, 70.34; H, 6.21; N, 8.63; O, 4.93; S, 9.59. Found: C, 70.32; H, 6.20; N, 8.62; O, 4.92; S, 9.58%;

4-(4-chlorophenyl)-9,10-dimethyl-4)-3,4,6,7-tetrahydro-1Hbenzo[6,7]cyclohepta[1,2-d]pyrimidine-2(5H)-thione(4f): Yield 75%; m.p. 80-81 ^{0}C; MS, m/z (%): 368(100). IR (KBr, cm^{-1}): 3388, 3196 (2NH), 1196 (C=S); ^{1}H NMR ($CDCl_3$), δ 7.40 (d, 2H, Ar-H), 7.30 (s, 2H, Ar-H), 6.99(s, 1H, Ar-H), 6.90(s, 1H, Ar-H), 5.10 (s, 1H, Pyrimidine-H), 2.85 (t, 2H, 6- CH_2), 2.34 (s, 6H, 8,9-di-CH_3), 2.00 (t, 2H, -4CH_2); 1.80 (q, 2H, 5 CH2). Anal. Calcd for $C_{21}H_{21}ClN_2S$: C, 68.37; H, 5.74; Cl, 9.61; N, 7.59; S, 8.69. Found: C, 68.35; H, 5.72; Cl, 9.60; N, 7.57; S, 8.68%;

4-fluoro-9,10-dimethyl-3,4,6,7-tetrahydro-1H-benzo[6,7]cyclohepta[1,2-d]pyrimidine-2(5H)-thione(4g): Yield 83%; m.p. 82-83 ^{0}C; MS, m/z (%): 352(100). IR (KBr, cm^{-1}): 3423, 3299 (2NH), 1222 (C=S); ^{1}H NMR ($CDCl_3$), δ 7.30 (s, 2H, Ar-H), 7.26 (s, 2H, Ar-H), 6.99(s, 1H, Ar-H), 6.90 (s, 1H, Ar-H),5.10 (s, 1H, Pyrimidine-H), 2.85 (t, 2H, 6- CH_2), 2.34 (s, 6H, 8,9-di-CH_3), 2.00 (t, 2H, -4CH_2); 1.80 (q, 2H, 5 CH2). Anal. Calcd for $C_{21}H_{21}N_2SF$: C, 71.56; H, 6.01; F, 5.39; N, 7.95; S, 9.10. Found: C, 71.55; H, 6.00; F, 5.38; N, 7.94; S, 9.09%.

9,10-dimethyl-4-(3-Nitrophenyl)**-3,4,6,7-tetrahydro-1H-benzo[6,7]cyclohepta[1,2-d]pyrimidine-2(5H)-thione (4h):** Yield 79%; m.p. 88-90 ^{0}C; MS, m/z (%): 379(100). IR (KBr, cm^{-1}): 3422, 3196 (2NH), 1216 (C=S); ^{1}H NMR ($CDCl_3$), δ 7.7 (d, 2H, Ar-H), 7.60 (d, 2H, Ar-H), 6.99 (s, 1H, Ar-H), 6.90 (s, 1H, Ar-H), 5.10 (s, 1H, Pyrimidine-H), 2.85 (t, 2H, 6- CH_2), 2.34 (s, 6H, 8,9-di-CH_3), 2.00 (t, 2H, -4CH_2); 1.80 (q, 2H, 5 CH2). Anal. Calcd for $C_{21}H_{21}N_3O_2S$: C, 66.47; H, 5.58; N, 11.07; O, 8.43; S, 8.45. Found: C, 66.44; H, 5.56; N, 11.07; O, 8.42; S, 8.43%;

9,10-dimethyl-4-(pyridin-3-yl-3,4,6,7-tetrahydro-1H-benzo[6,7]cyclohepta[1,2-d]pyrimidine-2(5H)-thione(4i): Yield 82%; m.p. 180-182 ^{0}C; MS, m/z (%): 335(100). IR: (KBr, cm^{-1}): 3423, 3199 (2NH), 1223 (C=S); ^{1}H NMR ($CDCl_3$), δ 8.60 (s, 1H, Pyridine-H), 8.50(d, 1H, Pyridine-H), 7.50 (d, 1H, Pyridine H),7.40 (t, 1H, - Pyridine H),6.99 (s, 1H, Ar-H), 6.90 (s, 1H, Ar-H), 5.25 (s, 1H, Pyrimidine-H), 2.85 (t, 2H, 6- CH_2), 2.34 (s, 6H, 8,9-di-CH_3), 2.00 (t, 2H, -4CH_2); 1.80 (q, 2H, 5 CH2). Anal. Calcd for $C_{20}H_{21}N_3S$: C, 71.61; H, 6.31; N, 12.53; S, 9.56. Found: C, 71.60; H, 6.30; N, 12.52; S, 9.55%;

9,10-dimethyl-4-(thiophen-2yl)-3,4,6,7-tetrahydro-1H-benzo[6,7]cyclohepta[1,2-d]pyrimidine-2(5H)-thione(4j): Yield 68%; m.p. 130-132 ^{0}C; MS, m/z (%): 340(100). IR (KBr, cm^{-1}): 3449, 2945 (2NH), 1200 (C=S); ^{1}H NMR ($CDCl_3$), δ 7.40 (d, 1H, thiophene-H), 6.99(s, 1H, Ar-H), 6.90(s, 1H, Ar-H), 6.78 (s, 1H, thiophene-H), 6.70 (s, 1H, thiophene -H), 5.10 (s, 1H, Pyrimidine-H), 2.85 (t, 2H, 6- CH_2), 2.34 (s, 6H, 8,9-di-CH_3), 2.00 (t, 2H, -4CH_2), 1.80 (q, 2H, 5 CH2). Anal. Calcd for $C_{19}H_{20}N_2S_2$: C, 67.02; H, 5.92; N, 8.23; S, 18.83. Found: C, 67.00; H, 5.87; N, 8.21; S, 18.82%;

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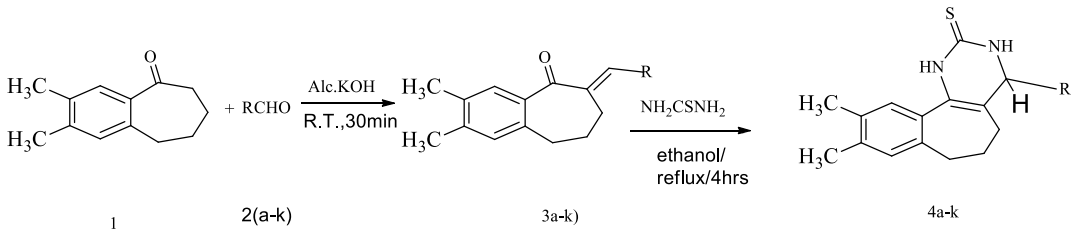
E)-9, 10-dimethyl-4-styryl-3,4,6,7-tetrahydro-1H-benzo[6,7]cyclohepta[1,2- d]pyrimidine-2(5H) -thione(4k): Yield 66%; m.p. 115-117 ^{0}C; MS, m/z (%): 360(100). IR (KBr, cm^{-1}): 3413, 3198 (2NH), 1211 (C=S); ^{1}H NMR ($CDCl_3$), δ 7.20-7.40 (m, 5H, Ar-H), 6.99(s, 1H, Ar-H), 6.90 (s, 1H, Ar-H), 6.80(d, 1H, ethylenic-H), 6.75(d, 1H, ethylenic –H), 3.65 (s, 1H, Pyrimidine-H), 2.85 (t, 2H, 6- CH_2), 2.34 (s, 6H, 8,9-di-CH_3), 2.00 (t, 2H, -4CH_2), 1.80 (q, 2H, 5 CH2). Anal. Calcd for C_{23} $H_{24}N_2S$: C, 76.63; H, 6.71; N, 7.77; S, 8.89. Found: C, 76.59; H, 6.69; N, 7.76; S, 8.88 %;

Scheme –I



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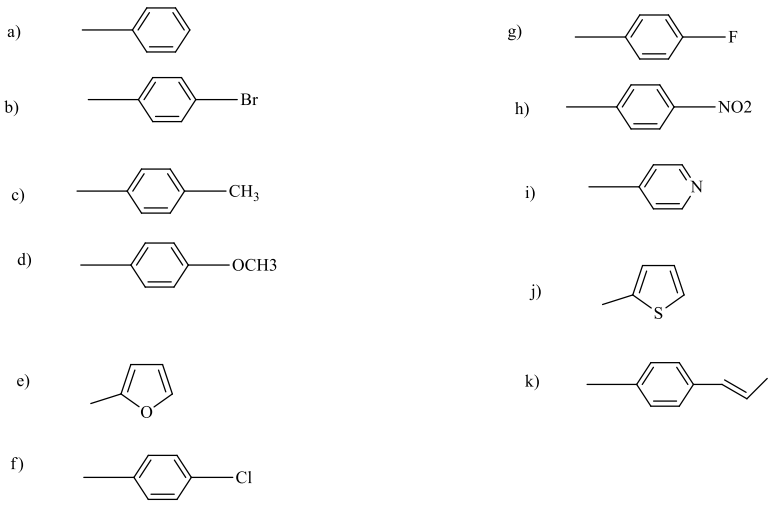

RESULTS AND DISCUSSION

Synthesis & characterization:

2, 3-dimethyl 6, 7, 8, 9-tetrahydro-5-H-benzo cyclohepten-5-one **1** was synthesized according to the reported [14] procedure. 2, 3-dimethyl-6-Arylidene-6, 7, 8, 9 tetrahydrobenzocyclohepten-5-one [10] **3** was obtained by the condensation of **1** with appropriate aromatic aldehydes (**2** a-k). In the 1H NMR spectrum of enone **3** the olefinic proton (= CH-Ar) was appeared at δ 7.80.According to reported procedure [3] compound **3** (a-k**)** refluxed with thiourea in the presence of alc.KOH afforded the corresponding thioxo pyrimidine derivatives **4**(a-k) (scheme –I).

In the ^{1}HNMR Spectrum of compound **4,** appearance of a characteristic proton at δ 5.10 ppm confirms the formation of pyrimidine-2-thione ring. Further the structure was confirmed by absence of olefinic proton at δ 7.80ppm. The aryl protons resonate as multiplets in the range of δ 6.80-7.60. The proton signals of methyl groups and aliphatic protons appeared in the aliphatic region. The structures were also confirmed from their IR spectra in which N-H stretching frequencies were observed. These Compounds were also confirmed by mass spectra.

Biological activities:

Anti cancer screening:

Anti cancer activity screening for the synthesized compounds utilizing different cell lines, was carried out according to the procedure as given below in materials and methods.

The obtained results (Table I) represent concentrations of the used investigated compounds resulting in growth inhibition of 50 %(**IC50)** for the tested human cancer cell lines. From the data it has been noticed that, the selected compounds **4g, 4h, 4i, 4j, 4k** are showing better activity.

Cytotoxic results of Thiones:

Table I: IC_{50} values of compounds determined by MTT method

S. No	Test compound	IC50 values (µM)				
		HeLa	B16-F10	SKOV3	MCF-7	CHO-K1
1	**4a**	NA	25.93±0.08	14.20±2.98	15.03±0.87	37.39±1.23
2	**4b**	NA	29.31±0.75	12.22±0.48	14.31±0.23	NA
3	**4c**	NA	34.22±0.34	10.36±0.36	13.91±0.49	NA
4	**4d**	NA	34.86±3.16	9.73±0.33	17.44±1.62	NA
5	**4e**	8.24 ± 1.0	14.13 ± 0.41	11.31 ± 0.53	**8.21 ± 0.70**	13.19 ± 0.33
6	**4f**	23.64 ± 0.26	36.91 ± 0.10	16.75 ± 0.95	11.42 ± 0.21	14.49 ± 1.0
7	**4g**	11.82 ± 0.75	13.70 ± 0.91	9.46 ± 0.89	**8.62 ± 0.02**	7.82 ± 0.25
8	**4h**	7.92 ± 0.91	14.44 ± 0.44	12.71 ± 0.61	**7.45 ± 1.0**	9.58 ± 0.88
9	**4i**	7.09 ± 0.09	11.72 ± 0.93	12.59 ± 0.21	**8.81 ± 0.04**	10.62 ± 0.30
10	**4j**	**3.82 ± 0.82**	12.35 ± 0.06	**7.26 ± 0.44**	**8.28 ± 0.64**	5.06 ± 0.75
11	**4k**	**3.42 ± 0.86**	13.16 ± 0.70	**7.45 ± 0.85**	**7.66 ± 0.73**	12.23 ± 0.59
Standard Drug Doxorubicin		0.8 ± 0.71	0.7 ± 0.56	**0.8 ± 0.63**	**2.0 ± 0.81**	-
Mitomycin C		-	-	-	-	13.1 ± 0.68

NA: No Activity.

Cell lines:

1. HeLa Homo sapiens cervix adenocarcinoma
2. B16-F10 Mouse skin melanoma (ATCC® CRL 6475™)
3. SKOV3 Human Ovarian cancer (ATCC® HTB 77™)
4. MCF7 Human Breast Adenocarcinoma ((ATCC® HTB-22™)
5. CHO-K1-Chinese hamster ovary cells ,Normal Cell line (ATCC® CCL-61™

Structure activity relationships (SAR studies):

From the above obtained results (Table I), we can determine structure activity relationships as below.

In this work anticancer activity is due to the presence of thio pyrimidine ring compound. By introducing $–NO_2$ (**4h**) group increases the activity against Adenocarcinoma cell lines. Compounds **4e, 4g, 4h, 4i, 4j** and **4k** are showing good to moderate activity against MCF7 (human breast adenocarcinoma cell lines).Introducing conjugation on phenyl substitution (**4k**) activity increases towards Hela (cervix adenocarcinoma) cell lines. Thiophene substituent shows better activity than furan substituent towards HeLa cell lines.

CONCLUSIONS

From the cytotoxicity evaluation, it is clear that compounds **4j, 4k** showed maximum activity against He La (human tumor cell) cell lines. Other compounds, **4e, 4g, 4h, 4i, 4j** and **4k** are showing good to moderate activity against MCF7 (human breast adeno carcinoma cell lines).From the data it is clear that pyrimidine ring fused to benzosuberone ring is essential for anticancer activity and the difference in activity is mainly due to the substituents in the phenyl group of the molecule.

These results indicate that these compounds may have therapeutic potential as templates for developing a new drug which will be useful to treat cancer.

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