ISSN: 0975-766X

Available Online through
www.ijptonline.com

Research Article

DESIGN, SYNTHESIS AND ANTICANCER ACTIVITY OF SOME NEW PYRIMIDINE DERIVATIVES

Prof. P Venkateswara Rao[1*], Prof Y Rajendra Prasad[2], Vijay Kotra[3], B Bhaskararao[2]

[1] Chebrolu Hanumaiah Institute of Pharmaceutical sciences, Guntur.
[2] University College of Pharmaceutical Sciences, Andhra University,Visakhapatnam.
[3] University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur.
Email:dr.pvrao2010@gmail.com

Received on 15-11-2010 *Accepted on 29-11-2010*

ABSTRACT: Some new pyrimidine derivatives were synthesized by reacting chalcones of 2-acetyl furan with guanidine hydrochloride in presence of alcohol. The synthesized compounds were characterized by IR and NMR spectral data and screened for anticancer activity. Some of these compounds showed moderate to considerable anticancer activity.

Keywords: Synthesis, Pyrimidines, Anticancer activity

INTRODUCTION

Compounds with pyrimidine structure are known to possess antimicrobial[1,2] anti-inflammatory[3], cytotoxic[4,5] and anticancer activities[6,7]. In the present study, some new pyrimidine derivatives **1-6** have been synthesized by the reaction of chalcones of 2-acetyl furan and guanidine hydrochloride. The structures of the various synthesized compounds are assigned on the basis of elemental analysis, IR and ^{1}HNMR. These compounds were also screened for anticancer activity.

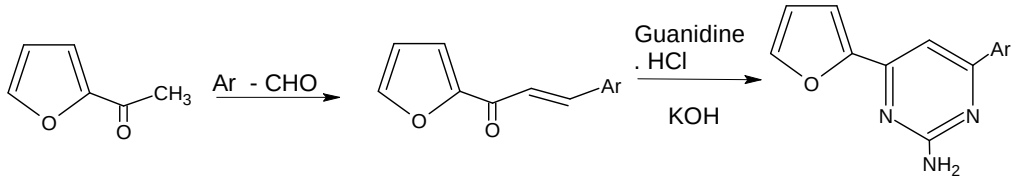
EXPERIMENTAL PART

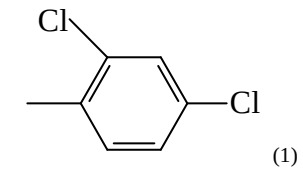
The melting points for all the compounds were determined in open capillaries using “Boitus melting point apparatus”, expressed in ^{0}C & are un-corrected. For column chromatography ACMES_Silicagel 100-200 mesh has been used. The solvent system is n-hexane in ethyl acetate in different proportions. The IR spectra of the

compounds were recorded on Perkin-Elmer BXFIFTIR spectrophotometer using KBr disks and the values were expressed in cm^{-1}. The ^{1}HNMR spectra of the compounds were recorded on Bruker-AMX 400Mhz Nmr spectrophotometer using TMS as an internal standard and the values are expressed in ppm. The Micro analysis of the synthesized compounds was performed on Carlo Erba EA-1108 elemental analyzer.

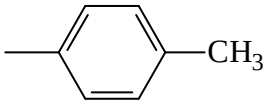
General procedure for the preparation of pyrimidine derivatines (1-6):

A mixture of chalcones of 2- acetylfuran (0.001mole) & guanidine hydrochloride (500mg) in absolute ethanol (10ml) were refluxed on a water bath for 6hrs. The solvent was allowed to evaporate completely and residue was poured into ice-cold water. The completion of reaction was established by the TLC using Silicagel-G. After completion of reaction, the reaction mixture was poured into crushed ice with constant stirring. The solid that separated was filtered, dried and it was purified by column chromatography on silicagel-G using ethyl acetate and n-hexane mixture as the mobile phase. The purified pyrimidine derivatives were obtained as light to bright yellow fine powder.

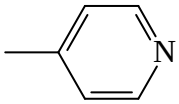




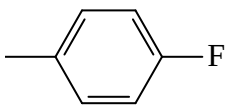
(1)



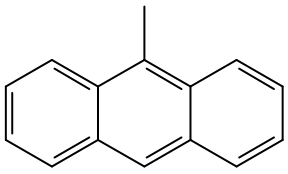
(2)



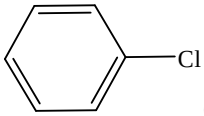
(3)



(4)



(5)



(6)

Scheme-1: Synthesis of some new pyrimidine derivatives (1-6).

Table-1: Elemental analysis of the synthesized compounds:

Compounds	Molecular formula	M.P	Yield	Elemental analysis (%)					
				C		H		N	
				Calculated	found	Calculated	found	Calculated	Found
1	$C_{14}H_9N_3OCl_2$	145	82%	55.08	55.38	2.95	2.75	13.77	13.57
2	$C_{15}H_{13}ON_3$	150	75%	71.71	71.67	5.17	5.27	16.73	16.83
3	$C_{13}H_{10}N_4O$	235	76%	65.56	65.54	4.23	4.20	23.56	23.52
4	$C_{22}H_{15}N_3F$	243	81%	66.16	66.14	3.96	3.93	7.11	7.08
5	$C_{22}H_{15}N_3O$	240	75%	80.73	80.53	4.58	4.28	12.84	12.94
6	$C_{14}H_{10}N_3OCl$	154	80%	61.99	61.50	3.69	3.82	15.49	15.69

Table-2: Spectral data of the Compounds (1-5).

Compound	IR (KBr, cm)	1HNMR ($CDCl_3$,ppm)
1)	3326(NH2),1638(C=N) 1578(C=C) ,892(C-Cl)	5.78(2H,S,-NH_2), 6.62(1H,m,C-4^1-H) 7.62(1H,S,-C-3^{11}-H), 7.64(1H,d,C-5^1-H) 7.54(1H,d,C-5^{11}-H), 7.41(1H,d,C-6^{11}-H) 7.39(1H,d,C-3^1-H) , 7.35(1H,S,C-5-H)
2)	3335(-NH_2),1632(C=N) 1576(C=C)	2.46(3H,S,Ar-CH_3),5.25(2H,S,-NH_2),6.67(1H,m,C-4^1-H),7.45(1H,S,C-5-H), 8.06(2H,d,C-3^{11}-H,C-5^{11}-H), 7.36(2H,d,C-2^{11}-H,C-6^{11}-H) 7.71(1H,d,C-5^1),7.60(1H,d,C-3^1H)
3)	3442,3355(NH_2), 1575 (C=N), 1526 (C=C), 1365 (C-N)	6.55-6.54(1H,m,C-4'H), .16(1H,d,J=6Hz,C-3'H)7.26 (1H,d,J=6Hz,C-5'H),7.46 (1H, d, J=7.8Hz, C-3''H& 5''H), 7.58 (1H,d,J=15Hz Ar-CH=).
4)	3468, 3318 (NH_2), 1599 (C=N), 1510 (C=C), 1349 (C-N), 1219 (C-F)	5.63 (2H, s, C-4'-NH_2), 5.21 (2H, s, C-2-NH_2), 6.64 (2H, d, J=8.4 Hz, C-3'), 7.19 (2H, dd,J=9.2 Hz, C-2" and 6"-H), 7.37 (1H, s, C-5-H), 8.084 (2H, dd, J=8.8 Hz, J=8.6 Hz, C-3" and 5"-H)
5)	3328(-NH_2),1642(C=N) 1587(C=C)	5.85(2H,S,-NH_2),6.61(1H,m,C-4^1-H) 7.60(1H,S,C-5-H),8.06(1H,d,C-5^1-H) 7.78(1H,d,C-3^1H,7.22-7.55(9H,m,Ar-H)
6)	3326(NH2),1638(C=N) 1578(C=C) ,892(C-Cl)	5.78(2H,S,-NH_2), 6.62(1H,m,C-4^1-H) 7.62(1H,S,-C-3^{11}-H), 7.64(1H,d,C-5^1-H) 7.54(1H,d,C-5^{11}-H), 7.41(1H,d,C-6^{11}-H) 7.39(1H,d,C-3^1-H) , 7.35(1H,S,C-5-H)

ANTICANCER ACTIVITY

The Synthesized Pyrimidine derivatives were tested for anti-cancer activity on DU-145 cell lines(prostate cancer) by MTT based cytotoxicity assay[8,9].

MTT based cytotoxicity assay

MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] based cytotoxicity assay is based on the ability of a mitochondrial dehydrogenase enzyme from viable cells to cleave the tetrazolium rings of the pale yellow MTT and form dark blue formazan crystals which is largely impermeable to cell membranes, thus resulting in its accumulation within healthy cells. The number of surviving cells is directly proportional to the level of the formazan created.

Cell proliferation assay was carried out by MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] cell proliferation assay kit (Roche applied sciences, Germany). Equal number of DU-145 cells were seeded in each well of 96-well microplate and incubated at 37°C, in presence of 5% CO_2. The cells were treated with test substances at various concentrations for 72 hrs. Culture medium was renewed at every 24 hrs with the test substances. In vehicle control culture wells, a maximum of 0.5% DMSO was added. After 72 hrs treatment , 5 µl of MTT reagent(R&D systems USA) along with 45µl of phenol red and FBS free DMEM (sigma Life Science, USA) was added to each well and incubated for 4 hrs at 37°C in presence of 5% CO_2. Thereafter 50 µl of solublization buffer (R&D systems, USA) was added to each well to solubilize the coloured formazan crystals produced by the reduction of MTT. After 24 hrs the optical density was measured at 550 nm using microplate reader (BioRad, USA). The results (mean O.D.± SD) obtained from quadruplicate wells were used in calculation to determine the cytotoxicity (50% inhibitory concentration, IC_{50}) of the test compounds.

Formula for calculation:

$$\% \text{ inhibition} = \frac{\text{Control O.D.} - \text{Sample O.D.}}{\text{Control O.D.}} \times 100$$

The IC_{50} values of newly synthesized pyrimidine derivatives were shown in table 3.

Table-3: Anticancer activity of pyrimidine derivatives on DU-145 cell lines.

S.No.	CompoundS	IC50 for cell proliferation (50µg/ml) DU-145
1.	COMPOUND-1	9.56
2.	COMPOUND-2	11.16
3.	COMPOUND-3	21.10
4.	COMPOUND-4	13.54
5.	COMPOUND-5	10.37
6.	COMPOUND-6	8.45

RESULTS AND DISCUSSION

The IC50 values for pyrimidines revealed that they are not having any significant anticancer activity against cell lines (DU-145). In the tested compounds compound 3 possess markable activity, however these compounds need to be tested on other cancer celllines inorder to predict their activity and usefulness.

REFERENCES

1. M. L Edwards , D.M. Stemerick and P.S. Sunkara, J. Med. Chem., 1998, vol33, pp1948.
2. Y. Rajendraprasad, P. Ravi kumar, , CH. Asha Deepti, and M. Venkataramana, Asian J. Chem., 2007, vol19(6), pp4799.
3. J.F.Ballesteros, M.J.Sanz, A.Ubeda, M.A.Miranda, S.Iborra, M.Priya and M.J. Alcraz, J.Med.Chem., 1995, Vol 38, PP 2794.
4. C.C. Yit and N.P. Das, Cancer. Lett. 1994, vol82, pp65.
5. Y. Satomi. Int. J. Cancer, 1993, vol55, pp506.

6. L.W.Wattenberg, J.B. Coccia and A.R. Galhaith, Cancer. Lett. 1994, vol83, pp165.
7. A.T.Dinkova-Kostova, C. Abeygunawardana and P.Talalay, J.Med. Chem. 1998, vol 41, pp5287.
8. American Cancer society, Cancer facts and figures(2002)
9. American Cancer society, Cancer facts and figures.

Corresponding Author*

Dr.P.Venkateshwar Rao*

Chebrolu Hanumaiah Institute of Pharmaceutical sciences, Guntur.

Email: *dr.pvrao2010@gmail.com*