SYNTHESIS AND ANTI-CANCER ACTIVITY OF SOME NEW PYRIMIDINE DERIVATIVES

B. RAMESH[1]*, S BABITHA[2]

1 Department of Pharmaceutical Chemistry, Sree Siddaganga College of Pharmacy, B.H. Road, Tumkur-572102. Karnataka, India.

2 Department of Pharmacology, Sree Siddaganga College of Pharmacy, B.H. Road, Tumkur-572102. Karnataka, India.

Summary

Some new pyrimidine derivatives were synthesized by reacting chalcones of 2-acetyl thiophene with guanidine hydrochloride in the presence of alcohol. The synthesized compounds were identified by spectral data and screened for anti-cancer activity. Some of these compounds showed moderate to considerable anti- cancer activity.

Key words: Synthesis, Pyrimidines, Anti- cancer activity.

Introduction

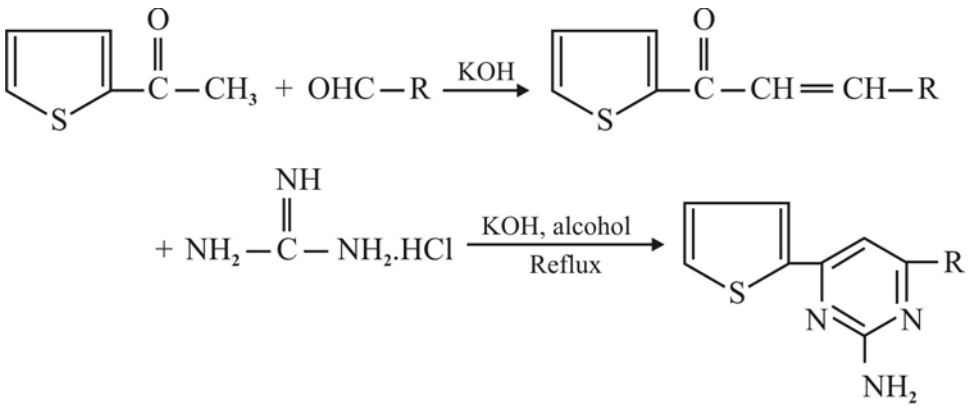
Compounds with pyrimidine structures are known to possess antimicrobial[1,2] anti-inflammatory[3], cytotoxic,[4,5] anti-cancer activities[6,7]. In the present study some new pyrimidine derivatives (1 to 5) have been synthesized by the reaction of chalcones of 2-acetyl thiophene and guanidine hydrochloride.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

Experimental

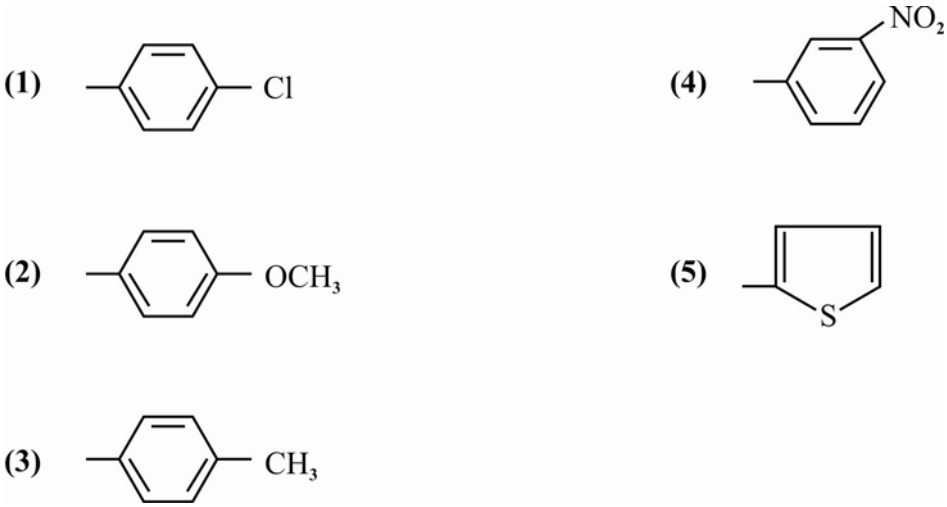
Melting points were determined on a capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra was recorded in the indicated solvent on Bruker WM 400 MHz spectrometer with TMS as internal standard. Infrared spectra were recorded in KBr on Perkin-Elmer AC-1 spectrophotometer. Microanalyses were performed on Carlo Erba EA-1108 element analyzer and were within the ± 0.5% of the theoretical values. Column chromatography was performed on silica gel (Merck, 60-120 mesh).

General procedure for the preparation of pyrimidine derivatives (1-5)

A mixture of chalcones of 2-acetyl thiophene (0.001 mol) and guanidine hydrochloride (500 mg) in absolute ethanol (10 ml) were reflexed on a waterbath for 6 hours. The solvent was completely evaporated and the residue was poured into ice cold water. The precipitated solid was collected by filtration and crystallized from suitable solvent to give the pyrimidine derivative.



(1-5)



Scheme 1 : Synthesis of some new pyrimidine derivatives

Table 1. Physical data of compounds (1-5)

Compound	*M.F.*	*M.P (°C)*	*Yield (%)*	Elemental analyses (%)					
				C		H		N	
				Calcd	Found	Calcd	Found	Calcd	Found
(1)	$C_{14}H_{10}SN_3Cl$	130	81	50.00	50.06	35.40	35.56	14.28	14.20
(2)	$C_{15}H_{13}OSN_3$	160	78	44.11	44.06	38.23	38.17	11.20	11.16
(3)	$C_{15}H_{13}SN_3$	95	77	45.54	45.45	40.01	39.38	12.14	12.10
(4)	$C_{14}H_{10}O_2N_4S$	181	62	56.42	56.37	3.38	3.35	18.80	18.78
(5)	$C_{12}H_9N_3S_2$	202	90	55.65	55.59	3.50	3.47	16.22	16.20

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

Compound	***IR (KBr, cm^{-1})***	^{1}H NMR ($CDCl_3$, ppm)
(1)	3342 (–NH_2), 1628 (C=N), 1580 (C=C), 856 (C–Cl), 652 (C–S).	5.35 (2H, brs, –NH_2), 7.16 (1H, m–C–4^{11}–H), 7.79 (1H, d, C–5^{11}–H), 7.51 (1H, d, C–3^{11}–H), 7.99 (2H, d, C–3^{1}–H, C–5^{1}–H), 7.45 (2H, d, C–2^{1}–H, C–6^{1}–H), 7.31 (1H, S, C–5–H).
(2)	3345 (–NH_2), 1625(C=N), 1590 (C=C), 1165 (–OCH_3), 646 (C–S).	3.89 (3H, S, –OCH_3), 7.19 (1H, m, C–4^{11}–H), 7.89 (1H, d, C–5^{11}–H), 7.69 (1H, d, C–5–H), 7.59 (1H, d, C–3^{11}–H), 8.01 (2H, d, C–3^{1}–H, C–5^{1}–H), 7.03 (2H, d, C–2^{1}–H, C–6^{1}–H).
(3)	3350 (–NH_2), 1630 (C=N), 1580 (C=C), 662 (C–S).	5.35 (2H, S–NH_2), 7.15 (1H, m, C–4^{11}–H), 7.80 (1H, d, C–5^{11}–H), 7.51 (1H, d, C–3^{11}–H), 7.99 (2H, d, C–3^{1}–H, C–5^{1}–H), 7.45 (2H, d, C–2^{1}–H, C–6^{1}–H), 7.32 (1H, S, C–5–H), 2.15 (3H, S, –CH_3).
(4)	3335 (–NH_2), 1635 (C=N), 1575 (C=O), 1510 (N=O), 1330 (N…O).	5.19 (2H, br, S, NH_2), 7.17 (1H, m, Ar–H), 7.40 (1H, S, C–5–H), 7.52 (1H, d, Ar–H), 7.66 (1H, t, Ar–H), 7.82 (1H, d, Ar–H), 8.40 (2H, m, Ar–H), 8.91 (1H. S, Ar–H).
(5)	3330 (–NH_2), 1635 (C=N), 1570 (C=C), 680 (C–S).	5.10 (1H, brS, NH_2), 7.14 (2H, m, Ar–H), 7.38 (1H, S, C–5–H), 7.47 (2H, d, Ar–H), 7.76 (2H, d, Ar–H).

Anticancer activity

Five compounds (1-5) were screened for anticancer activity (prostate cancer[8]) by MTT based cytotoxicity assay[9]. Du-145 cell lines were used for the experiment. The cell lines were obtained national center for cell science (NCCS), Pune (India). The IC50 values of newly synthesized pyrimidine derivatives (1-5) were shown in table 3.

Table-3. Anti-cancer activity of pyrimidine derivatives on Du-145 cell lines

Compound	IC50 for cell proliferation (50 μg/mL) Du-145
1	11.96
2	13.04
3	5.12
4	18.48
5	17.39

Results And Discussion

The screening results revealed that they are not having any significant anticancer activity against the cell line (Du-145) tested. However, these compounds need to be tested on other cancer cell lines in order to predict their activity and usefulness.

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References

1. M.L. Edwards, D.M. Stemerick and P.S. Sunkara, J. Med. Chem., **33**, 1948 (1998).
2. Y.Rajendra Prasad, P.Ravi Kumar, Ch. Asha Deepti and M.Venkata Ramana, Asian J. Chem., **19(6)**, 4799 (2007).
3. J.F.Ballesteros, M.J.Sanz, A.Ubeda, M.A.Miranda, S.Iborra, M.Paya and M.J.Alcaraz, J. Med. Chem., **38**, 2794 (1995).
4. C.C. Yit and N.P. Das, Cancer. Lett., **82**, 65 (1994).
5. Y.Satomi. Int. J. Cancer, **55**, 506 (1993).
6. L.W.Wattenberg, J.B.Coccia and A.R.Galhaith, Cancer. Lett., **83**, 165 (1994).
7. A.T.Dinkova-Kostova, C.Abeygunawardana and P.Talalay, J. Med. Chem., **41**, 5287 (1998).
8. American Cancer Society, Cancer facts and figures (2002) (http://www.cancer.org)
9. Mosmann, T., J.Immunol Methods. 65 (1-2): 55-63.