SYNTHESIS AND ANTI-MICROBIAL ACTIVITY OF SOME NEW PYRIMIDINE DERIVATIVES

B. RAMESH*, Dr. Y.RAJENDRA PRASAD, SYED MANSOOR AHMED.
Department of Pharmaceutical Chemistry, 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 antimicrobial activity. Some of these compounds showed moderate to considerable antimicrobial activity.

Key words: Synthesis, Pyrimidines, Antimicrobial activity.

Introduction

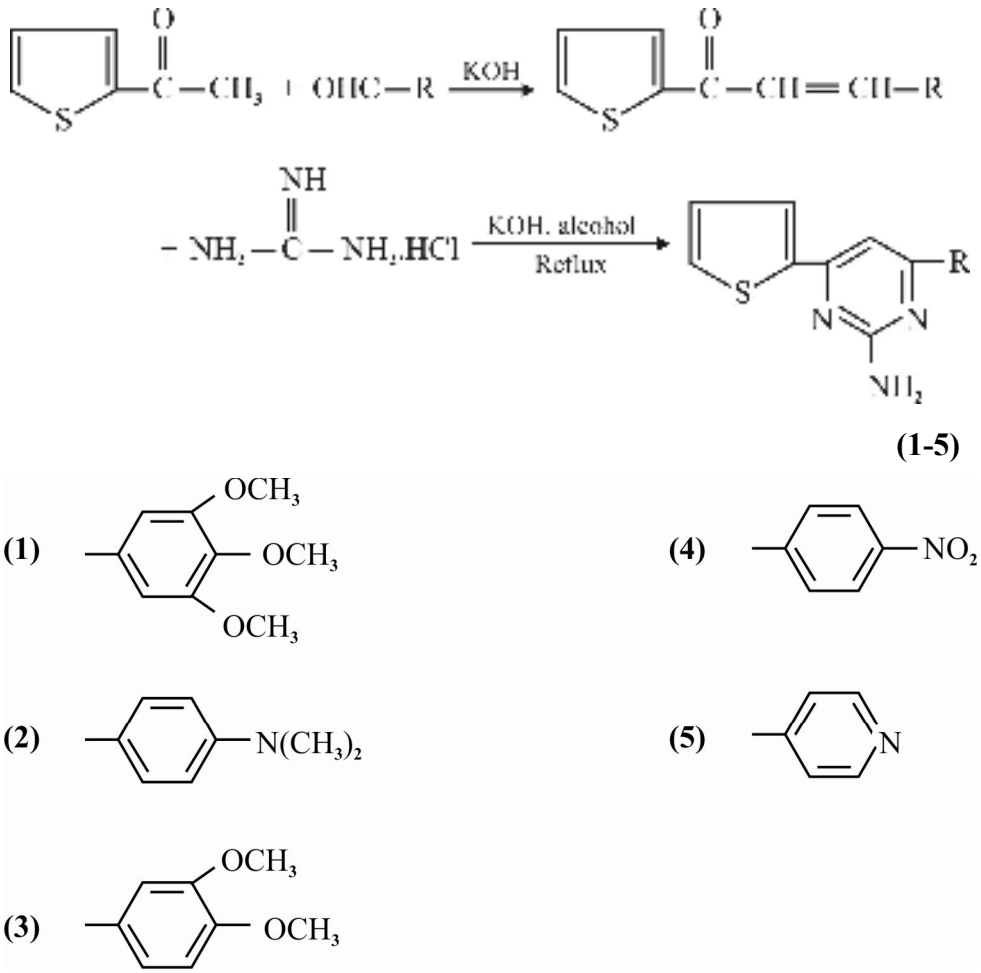
Compounds with pyrimidine structures are known to possess antimicrobial[1,2] anti-inflammatory[3], cytotoxic,[4,5] anti-cancer activities[6,7]. In the present study some new pyrimidine derivatives (1 to 5) have been synthesized by the reaction of chalcones of 2-acetyl thiophene and guanidine hydrochloride. 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-inflammatory 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.



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)	$C_{17}H_{17}O_3SN_3$	150	72	41.46	41.45	41.46	41.39	9.72	9.81
(2)	$C_{16}H_{16}SN_4$	120	76	42.10	42.16	42.10	42.08	14.10	14.14
(3)	$C_{16}H_{15}N_3SO_2$	143	82	61.39	61.34	4.83	4.79	13.42	13.41
(4)	$C_{14}H_{10}O_2N_4S$	232	76	57.93	56.37	3.44	3.35	16.55	16.23
(5)	$C_{13}H_{10}N_4S$	198	64	61.47	61.41	3.96	3.93	22.05	22.04

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

Compound	IR (KBr, cm^{-1})	^1H NMR ($CDCl_3$, ppm)
(1)	3361 ($-NH_2$), 1601 (C=N), 1572 (C=C), 1119 ($-OCH_3$), 704 (C–S).	5.22 (2H, brs, $-NH_2$), 3.91-3.99 (9H, S, =3X–OCH_3), 7.17 (1H, m, C–4^{11}–H), 7.80 (1H, d, C–5^{11}–H), 7.50 (1H, d, C–3^{11}–H), 7.29 (2H, S, C–2^1–H, C–6^1–H), 7.30 (1H, S, C–5–H).
(2)	3338 ($-NH_2$), 1633 (C=N), 1588 (C=C), 1185 ($-N(CH_3)_2$), 660 (C–S).	3.10 (6H, S, $-N(CH_3)_2$), 5.40 (2H, brs, $-NH_2$), 7.15 (1H, m, C–4^{11}, H), 8.01 (2H, d, C–3^1–H, C–5^1–H), 6.75 (2H, d, C–2^1–H, C–6^1–H), 7.79 (1H, d, C–5^{11}–H), 7.48 91H, d, C–3^{11}–H), 7.28 (1H, S, C–5–H).
(3)	3414 ($-NH_2$), 1641 (C=N), 1519 (C=C), 1145 ($-OCH_3$), 735 (C–S).	3.94 (3H, S,C–3–OCH_3), 3.99 (3H, S, C–4–OCH_3), 5.23 (2H, brs, NH_2), 6.95 (1H, d, Ar–H), 7.13 (1H, t, Ar–H), 7.15 (1H, S, Ar–H), 7.31 (2H, S, C–5–H), 7.47 (1H, d, Ar–H), 7.60 (1H, d, Ar–H), 7.68 (1H, d, Ar–H).
(4)	3413 ($-NH_2$), 1605 (C=N), 1344 (C=O), 688 (N=O).	5.26 (2H, brs, NH_2), 7.17 (1H, m, Ar–H), 7.38 (1H, S, C–5–H), 7.52 (1H, d, Ar–H), 7.81 (1H, d, Ar–H), 8.20 (2H, d, Ar–H), 8.33 (2H, d, Ar–H).
(5)	3335 ($-NH_2$), 1635 (C=N), 1570 (C=C), 680 (C–S).	5.22 (2H, brs, NH_2), 7.16 (1H, m, Ar–H), 7.38 (1H, S, C–5–H), 7.51 (1H, d, Ar–H), 7.80 (1H, d, Ar–H), 7.90 (2H, d, Ar–H), 8.76 (2H, d, Ar–H).

Antimicrobial activity

Cup plate method[8,9] using Mueller-Hinton agar medium was employed to study the preliminary antibacterial activity of (1-5) against *B. pumilis, B. substilis, E. coli* and *P. vulgaris*. The agar medium was purchased from Hi media Laboratories Ltd., Mumbai, India. Preparation of nutrient broth, subculture, base layer medium, agar medium and peptone water was done as per the standard procedure. Each test compound (5 mg) was dissolved in 5 mL of dimethyl sulfoxide (1000 μg/mL). Volumes of 0.05 mL and 0.1 mL of each compound were used for testing.

Table 3. Antibacterial activity of the compounds (1-5)

Compound	Zone of inhibition (in mm)							
	B. substilis		***B. pumilis***		***E. coli***		***P. vulgaris***	
	0.05 mL	**0.1 mL**	**0.05 mL**	**0.1 mL**	**0.05 mL**	**0.1 mL**	**0.05 mL**	**0.1 mL**
Standard	28	33	31	32	25	27	28	31
Control	-	-	-	-	-	-	-	-
1	17	20	13	15	12	21	15	20
2	15	17	13	14	12	20	12	18
3	15	16	12	14	13	19	12	20
4	14	19	11	12	10	13	12	18
5	16	19	14	15	13	21	14	20

Control : (Dimethyl sulfoxide), Standard (Benzyl penicillin)

Table 4. Anti-fungal activity of the compounds (1-5)

Compound	Zone of inhibition (in mm)			
	A.niger		***P.Crysogenium***	
	0.05 mL	**0.1 mL**	**0.05 mL**	**0.1 mL**
Standard	25	28	23	27
Control	-	-	-	-
1	16	18	15	18
2	10	14	11	13
3	12	14	11	13
4	12	14	11	13
5	16	17	14	17

Control : (Dimethyl sulfoxide), Standard (Fluconozole)

Same cup plate method using PDA medium was employed to study the preliminary antifungal activity of **(1-5)** against *A. niger* and *P. crysogenium*. The PDA medium was purchased from Hi media Laboratories Ltd., Mumbai, India. Preparation of nutrient broth, subculture, base layer medium and PDA medium was done as per the standard procedure. Each test compound (5 mg) was dissolved in 5 mL of dimethyl sulfoxide (1000 μg/mL). Volumes of 0.05 mL and 0.1 mL of each compound were used for testing.

The cups each of 9 mm diameter were made by scooping out medium with a sterilized cork borer in a petri dish, which was streaked with the organisms. The solutions of each test compound (0.05 and 0.1 mL) were added separately in the cups and petri dishes and were subsequently incubated. Benzyl penicillin and fluconazole were used as standard reference drugs (200 and 500 μg/mL, respectively) and dimethyl sulphoxide as a control, which did not reveal any inhibition. Zone of inhibition produced by each compound was measured in mm and the results are presented in Tables 3 and 4.

Results and Conclusions

Antibacterial activity

The screening results revealed that the compounds (1-5) showed significant antibacterial activity at both 0.05 mL abd 0.1 mL concentration levels when compare with standard drug benzyl penicillin. It was found that compound 1 and 5 showed maximum activity. It is interesting to note that compound 1 and 5 is having dichloro and fluoro groups as pharmacophores respectively.

Antifungal activity

The screening results revealed that the compounds (1-5) showed significant antifungal activity at both 0.05 mL and 0.1 mL concentration levels when compared with standard drug fluconazol. In particular compounds 1 and 5 possessed maximum activity which may be due to the presence of dichloro and fluoro as pharmacophores respectively.

Acknowledgements

We are thankful to the Head, Sophisticated Instrumentation Facility, Indian Institute of Sciences, Bangalore for ^{1}H NMR spectra and to Sipra Laboratories, Hyderabad for IR spectra.

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. K. Bowden, A. Dal Pozzo and C.K. Duah, J. Chem. Res. (S)., 377 (1990).
9. H. W. Seely and P. J. Van Demark, Microbes in Action: A Laboratory Manual of Microbiology, D. B. Taraporewala Sons and Co, Bombay, (1975) pp. 55- 80.