RESEARCH PAPER

Accepted 30 January 1998
Received 5 September 1997
Indian J. Pharm. Sci., 1998, 60(3) pp. 136-139

Synthesis and antimicrobial evaluation of 5-oxoimidazolylaminopyrazole-4-carboxaldehydes and their Schiff's bases

BIPLAB DE AND G. V. S. RAMA SARMA*
Department of Pharmaceutical Chemistry,
J. S. S. College of Pharmacy, "Rocklands", P. B. No. 20,
Ootacamund - 643 001.

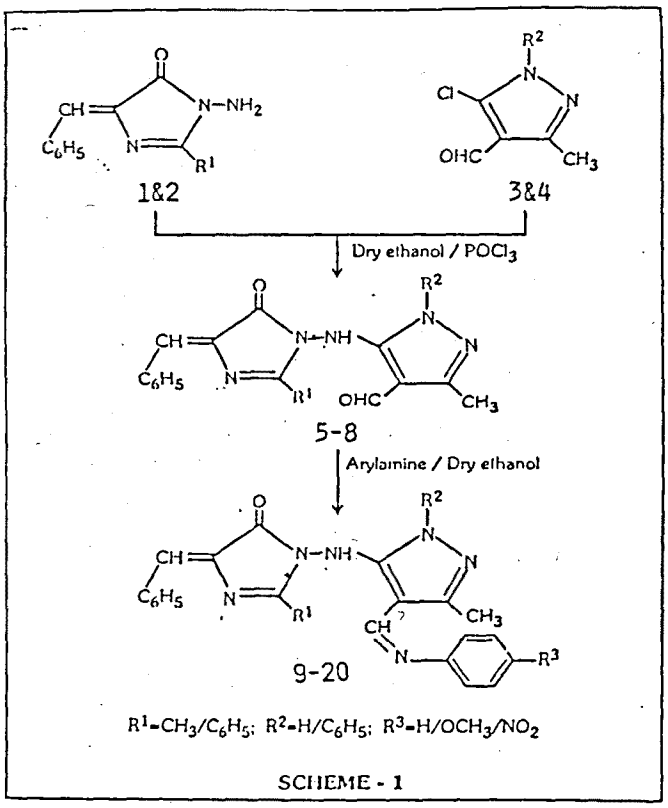
Condensation of 1-amino-4-benzylidene-2-methyl/phenylimidazolin-5 (4H)-ones (1&2) with 5-chloro-3-methyl-1-substituted pyrazole-4-carboxaldehydes (3&4) gave corresponding 5-(4-benzylidene-2-methyl/phenyl-5-oxoimidazolin -1-yl) amino -3-methyl-1-substituted pyrazole-4-carboxaldehydes (5-8). These were reacted with arylamines to afford corresponding Schiff's bases (9-20). All these compounds were characterized and evaluated for their antibacterial and antifungal activities. Some of them were found to exhibit significant antibacterial and antifungal activities.

PYRAZOLES are known to possess analgesic, antiinflammatory, antibacterial, antifungal, antineoplastic, antiallergic and hypoglycemic activities[1,2]. The pharmacological efficacy of imidazolones is also well known[3-5]. In view of these observations and in continuation of our search on imidazolones of biological and pharmacological significance[6-8], it was contemplated to synthesize some novel compounds containing both pyrazole and 5(4H)-imidazolone moieties interconnected through 'NH' bridge with a view to evaluate their possible biological and pharmacological properties. Synthesis of the title compounds was depicted in Scheme - 1.

Condensation of 1-amino-4-benzylidene-2-methyl/phenyl-imidazolin-5(4H)-ones (1 and 2)[9,10] and 5-chloro-3-methyl-1-substituted pyrazole-4-carboxaldehydes (3 and 4)[9,11] in dry ethanol using phosphorousoxychloride gave corresponding 5-(4-benzylidene-2-methyl/phenyl-5-oxoimidazolin-1-yl) amino-3-methyl-1-substituted pyrazole-4-carboxaldehydes (5-8). The products obtained were purified and characterized by spectral and analytical data. For instance, 1-amino-4-benzylidene-2-phenylimidazolin-5(4H)-one (2) on condensation with 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde (4) in dry ethanol using phosphorousoxychloride afforded yellowish red solid. It was purified by recrystallization from acetone and characterized as 5-(4-benzylidene-2-phenyl-5-oxoimidazolin-1-yl)-amino-3-methyl-1-phenylpyrazole-4-carboxaldehyde (8). Its IR(KBr) spectrum exhibited characteristic absorption bands at 3468(NH), 1710(C=O;imidazolone), 1660(C=O), 1650(CH=C) and 1625(C=N)cm^{-1}. Its PMR(DMSO-d_6) spectrum showed characteristic proton signals in δ ppm at 2.40 (s, 3H, CH_3), 7.25-8.12 (m, 15H, Ar-H), 8.25(bs, 1H, CH=C), 9.12(bs, 1H, NH, D_2O exchangeable) and 9.48 (s, 1H, CHO) and mass spectrum exhibited molecular ion peak at m/z 447 (23%).

Each of these carboxaldehydes (5-8) were than reacted separately with different arylamines in dry ethanol to furnish pale yellow to pale brown crystalline solids in reasonably good yields. They were purified and characterized as the respective 5-(4-benzylidene-2-methyl/phenyl-5-oxoimidazolin-1-yl) amino-3-methyl-1-substituted-4-(arylimino-methyl) pyrazoles (9-20). For example, reaction of 5-(4-benzylidene-2-methyl-5-oxoimidazoline-1-yl) amino-3-methyl-1-phenylpyrazole-4-carboxaldehyde (6) with 4-methoxyaniline in dry ethanol gave a pale brown solid characterized as 5-(4-benzylidene-2-methyl-5-oxoimidazolin-1-

*For Correspondence



SCHEME - 1

Synthesis and antimicrobial evaluation of 5-oxoimidazolylaminopyrazole-4-carboxaldehydes and their Schiff's bases

yl) amino-3-methyl-1-phenyl-4-(4 methoxypheny-liminomethyl) pyrazole (13). Its IR (KBr) spectrum showed peaks at 3450(NH), 1715(C=O, imidazolone), 1645(CH=C) and 1620(C=N)cm^{-1}. PMR (DMSO-d_6) spectrum displayed characteristic signals in δ ppm at 2.65 - 2.90 (bs, 6H, 2XCH_3), 3.61 (S, 3H, OCH_3), 6.85 - 7.62 (m, 14H, Ar-H), 7.84 (s, 1H, N=CH), 8.25 (bs, 1H, CH=C) and 9.12 (bs, 1H, NH, D_2O exchangeable). Mass spectrum recorded molecular ion peak at m/z 490 (38%). All the compounds were evaluated for their antibacterial and antifungal properties by standard method[12].

EXPERIMENTAL

Melting points were determined in open capillaries on an electrically heated block and are uncorrected. IR(KBr) spectra were recorded on Perkin-Elmer model-1600 spectrophotometer, PMR spectra on Jeol FX-100 FTNMR 100 MHz spectrophotometer using TMS as an internal standard and mass spectra on Jeol AX-500 double beam spectrophotometer.

The required 1-amino-4-benzylidene-2-substituted imidazolin-5(4H)-ones (1 and 2)[10] were prepared from the respective 4-benzylidene-2-substituted oxazolin-5(4H)-ones[9] by the reaction of hydrazine hydrate. Similarly, the required 5-chloro-3-methyl-1-substituted pyrazole-4-carboxaldehydes (3 and 4)[11] were obtained by formulation of appropriate 3-methyl-1-substituted pyrazole-5 (4H)-ones[9] using Vilsmeier-Haack reagent (DMF/$POCl_3$). 5-(4-Benzylidene-2-methyl/phenyl-5-oxoimidazolin-1-yl) amino-3-methyl-1-substituted pyrazole -4-carboxaldehydes (5-8).

An equimolar (0.2 mol) mixture of each of 1-amino-4-benzylidene-2-methyl / phenylimidazolin-5(4H)-ones (1 or 2)[9,10] and 5-chloro-3-methyl-1-substituted pyrazole-4-carboxaldehyde (3 or 4)[9,11] in dry ethanol (100 ml) was refluxed for 6-9 hrs in presence of phosphorousoxychloride (3 ml). The reaction mixture was cooled and poured onto crushed ice while stirring to get yellowish red solid which was filtered, washed, dried and purified by recrystallization from acetone.

5-(4-Benzylidene-2-methyl/phenyl-5-oxoimidazolin-1-yl)- amino-3-methyl-1-substituted-4-(aryliminomethyl)-pyrazoles (9-20).

An equimolar (0.01 mol) mixture of corresponding pyrazole-4-carboxaldehydes (9-12) and appropriate 4-substituted aniline in dry ethanol (50 ml) was refluxed for 4-6 h. The reaction mixture was cooled and poured onto crushed ice while stirring continuously. The resultant pale brown solid was filtered, washed, dried and purified by recrystallization from acetone.

Physical and analytical data of all the title compounds are presented in Table-1.

Bio-assay

Antibacterial activity of the compounds (in DMF) was determined by cup-plate method[12] at a concentration of 100 ug/ml against two gram-positive bacteria, *Bacillus subtilis*, *Staphylococcus aureus* and two gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa* using

Table - 1

Physical, analytical and antimicrobial data of compounds 5-20

Compd.	Substituents			Mol. Formula	MP	Nitrogen analysis	Antibacterial activity*				Antifungal activity*	
	R^1	R^2	R^3		°C	Obs(Calc.)	B.s	S.a	E.c	P.a	C.a	A.f
5	CH_3	H	-	$C_{16}H_{15}N_5O_2$	188	22.59 (22.65)	19	18	23	NA	NA	NA
6	CH_3	C_6H_5	-	$C_{22}H_{19}N_5O_2$	96	18.10 (18.18)	18	17	18	13	NA	NA
7	C_6H_5	H	-	$C_{21}H_{17}N_5O_2$	108	18.84 (18.87)	20	17	20	15	17	NA
8	C_6H_5	C_6H_5	-	$C_{27}H_{21}N_5O_2$	132	15.59 (15.66)	27	21	18	NA	11	NA
9	CH_3	H	H	$C_{22}H_{20}N_6O$	125	21.82 (21.88)	19	19	24	12	21	18
10	CH_3	H	OCH_3	$C_{23}H_{22}N_6O_2$	160	20.21 (20.29)	20	16	18	17	18	NA
11	CH_3	H	NO_2	$C_{22}H_{19}N_7O_3$	151	22.80 (22.84)	20	16	16	NA	19	NA
12	CH_3	C_6H_5	H	$C_{28}H_{24}N_6O$	134	18.22 (18.26)	19	NA	19	18	NA	NA
13	CH_3	C_6H_5	OCH_3	$C_{29}H_{26}N_6O_2$	142	17.06 (17.14)	17	NA	20	16	14	17
14	CH_3	C_6H_5	NO_2	$C_{28}H_{23}N_7O_3$	152	19.33 (19.41)	19	NA	15	NA	19	NA
15	C_6H_5	H	H	$C_{27}H_{22}N_6O$	90	18.74 (18.83)	20	17	16	17	NA	NA
16	C_6H_5	H	OCH_3	$C_{28}H_{24}N_6O_2$	129	17.60 (17.65)	23	19	17	17	17	19
17	C_6H_5	H	NO_2	$C_{27}H_{21}N_7O_3$	141	19.92 (19.96)	22	20	16	18	19	15
18	C_6H_5	C_6H_5	H	$C_{33}H_{26}N_6O$	107	16.01 (16.09)	24	20	21	21	NA	NA
19	C_6H_5	C_6H_5	OCH_3	$C_{33}H_{28}N_6O_2$	104	15.16 (15.22)	20	17	20	19	15	17
20	C_6H_5	C_6H_5	NO_2	$C_{33}H_{25}N_7O_3$	127	17.21 (17.28)	20	18	17	NA	NA	NA
Ampicillin		-	-	-	-	-	41	42	28	27	-	-
Amphotericin		-	-	-	-	-	-	-	-	-	27	26

Yields were between 50 and 80%. Satisfactory C&H analyses were also obtained. Compounds 5-8 were yellowish red and compounds 9-20 were pale yellow to pale brown. IR(KBr) spectra of all the compounds showed characteristic peaks (in cm^{-1}) for NH(3320-3480), C=O, imidazolone (1710-1730), CH=C (1645-1655), C=N (1610-1630) and in addition compounds 5-8 exhibited characteristic bands in cm^{-1} for C=O (1660-1680).

* Zone of inhibition in mm; B.s=B.subtilis; S.a=S.aureus; E.c=E.coli; P.a=P.aeruginosa; C.a=C. albicans; A.f=A. flavus; NA=Not active.

ampicillin (100 ug/ml) as standard while antifungal activity was determined, in similar way against *Candida albicans* and *Aspergillus flavus* employing amphotericin (100 ug/ml) as the standard. The results are presented in Table-1.

RESULTS AND DISCUSSION

Results reveal that some of these compounds elicited interesting antibacterial and antifungal activities, however not on par with that of the standards employed. Antibacterial data indicated that compound 8 was active against *B. subtilis* and *S. aureus* whereas compound 5 was active against *E. coli* while the rest of the compounds viz 6 and 7 in aldehydic series were moderately active. Among the Schiff's bases, many compounds exhibited appreciable action against all types of bacteria employed. Compound 18 was potent against all bacteria, followed by compounds 17,16 and 19. It could be observed that *P. aeruginosa* was less sensitive to the title compounds. Compounds 12-14 did not show any inhibition in the growth of *S. aureus* while the rest of compounds exhibited moderate to mild inhibition.

Antifungal activity studies reveal that out of the four compounds of aldehydic series, compounds 7 and 8 exhibited moderate and mild activities, respectively only against *C. albicans*. Among the twelve Schiff's bases, eight compounds were active against *C. albicans* while only five compounds were active against A. flavus. Compounds 10, 11 and 14 were active only against *C. albicans* and compounds 12, 15, 18 and 20 were completely ineffective against both the fungi. Interestingly, compound 9 was found to possess remarkable activity against both the fungi employed, while compound 17 was effective considerably against *C. albicans* and moderately against *A. flavus*, which was observed to be most sensitive to compound 16 and moderately sensitive to compounds 13 and 19. It could be observed, however that all these compounds were inferior in their antifungal activity as compared to the standard employed.

ACKNOWLEDGEMENTS

The authors wish to thank Jagadguru Sri Shivarathri Deshikendra Mahaswamigalavaru, Suttur Mutt, Mysore for the facilities, Mr. S. A. Dhanraj for his help in bioassay and Prof. B. Suresh, Principal, for his encouragement.

REFERENCES

1. Kamal, A., Reddy, A. V. N and Sattur, P. B., **Indian J. Chem.**, 1985, 24B, 414.
2. Basaif, S. A., Faidallah, H. M and Hasan, S. Y., **Indian J. Heterocycl. Chem.**, 1996, 6, 53.
3. Jolly, V. S. and Pathak, M., **J. Indian Chem. Soc.**, 1991, 68, 624.
4. Swarup, S., Saxena, V. K. and Chowdhary, S. R., **Indian J. Pharm. Sci.**, 1989, 52, 124.
5. Verma, M., Chaturvedi, A. K., Chandhari, A. and Parmar, S. S., **J. Pharm. Sci.**, 1974, 63, 1741.
6. Rama Sarma, G. V. S. and Reddy, V. M., **Indian J. Heterocycl. Chem.**, 1993, 3, 111.
7. Rama sarma. G. V. S. Suresh, B. and Reddy, V. M., **Indian Drugs**, 1997, 34, 17.
8. Rama Srama, G. V. S. and Reddy, V. M., **Indian J. Pharm. Sci.**, 1997, 59(5), 236.
9. Vogel, A. I., **Text book of Practical Organic Chemistry**, IVth ed., Longman Group Ltd., London, 1986, 882.
10. Baxi, A. J., Upadhyay, P. S., Joshi, H. D. and Parikh, A. R., **Indian J. Heterocycl. Chem.**, 1991, 1, 71.
11. Pawar, R. A. and Patil, A. A., **Indian J. Chem.**, 1994, 33B, 156.
12. **British Pharmacopoeia**, Pharmaceutical Press, London, 1953, 796.