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SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-ARYLOXY METHYL – 4-[-2'(BENZIMIDAZOLYL THIO) ACETAMIDE]-5-MERCAPTO-1,2,4-TRIAZOLES

B. SHIVKUMAR*, SHOBHARAM SAHU, T. Y. PASHA, R. H. UDUPI[a], A. R. BHAT[b], R. NAGENDRA RAO and A. VEERANAGOUD

Paul Ehrlich Laboratory, Dept. of Pharmaceutical Chemistry, S. C. S. College of Pharmacy, HARAPANAHALLI – 583131 (K. S.) INDIA
[a]Department of Pharmaceutical Chemistry, N. E. T. College of Pharmacy, RAICHUR – 584101 (K. S.) INDIA.
[b]Department of Pharmaceutical Chemistry, K. L. E.'s College of Pharmacy, J. N. M. C. Campus, BELGAUM – 584110 (K. S.) INDIA.

ABSTRACT

Aryloxy potassium dithiocarbazintates **(IV)** were prepared by reaction of aryloxy acid hydrazides **(III)** with alcoholic KOH and CS_2 , which when cyclised with 2-(benzimidazolyl thio) methyl acetic acid hydrazide **(V)** gave 3-aryloxymethyl-4-[2-(benzimidazolyl thio) acetamido]-5-mercapto-1,2,4-triazoles **(VI a-h)**.The structures of the new compounds were characterized on the basis of analytical and spectral data. Antimicrobial activities of synthesized compounds was evaluated and some of the compounds exhibited promising activity.

Key words: 3-Aryloxymethyl-4-[2-(benzimidazolyl thio) acetamido]-5-mercapto-1,2,4-triazoles , Antibacterial activity, Antifungal activity.

INTRODUCTION

Triazole is biologically potent heterocycle. Many of the triazole moiety containing drugs are clinically used for various ailments [1,2]. Triazoles are also reported to possess hypoglycemic [3], anti-inflammatory[4] and antifungal [5] activities. Benzimidazole containing heterocycles are reported to possess many useful activities like anti-inflammatory [6], anti-microbial [7] and antiviral [8] activities. In continuation of our work on triazoles[9,10], the present work was undertaken to synthesize some novel benzimidazolo-triazoles with the aim of obtaining compounds with view to enhance the activity of triazole derivatives.

* Author for correspondence; E-mail: drsk2007@yahoo.com

EXPERIMENTAL

The required aryloxy and benzimidazolo hydrazides were prepared from corresponding esters by the reaction with hydrazine hydrate following the reported procedure[11,12]. The aryloxy potassium dithiocarbazintates **(IV)** were prepared by treating aryloxy acid hydrazides **(III)** with alcoholic KOH and CS_2 , which on cyclisation with 2-(benzimidazolyl thio) methyl acetic acid hydrazide **(V)** yielded 3-aryloxymethyl-4-[2-(benzimidazolyl thio) acetamido]-5-mercapto-1,2,4-triazoles **(VI a-h)**.

Biological activity

All the synthesized compounds were subjected to antibacterial and antifungal activity by cup-plate method[13,14]. Anti-bacterial activity was evaluated against *Staphylococcus aureus* (gram +ve) and *Escherichia coli* (gram –ve) pathogens, Procaine penicillin and streptomycin were used as standard drugs, respectively. The results of the antibacterial activity are given in Table 2. Antifungal activity was tested against *Candida albicans* and *Aspergillus flavus*, Griseofulvum was used as a standard drug. The results of the antifungal study is given in Table 3.

Melting point of synthesized compounds was determined in open capillary method and were uncorrected.

Table 1. Physical data of synthesized compounds

Compound	M. F.	R	M.P. (^{o} C)	Yield (%)
(VI a)	$C_{18}H_{15}O_2N_6S_2Cl$	p-Cl	156	88
(VI b)	$C_{18}H_{15}O_4N_7S_2$	p-NO_2	167	75
(VI c)	$C_{19}H_{18}O_2N_6S_2$	o-CH_3	189	76
(VI d)	$C_{19}H_{18}O_2N_6S_2$	p-CH_3	147	79
(VI e)	$C_{18}H_{15}O_2N_6S_2Cl$	o-Cl	152	76
(VI f)	$C_{22}H_{18}O_2N_6S_2$	Phenyl	225	85
(VI g)	$C_{19}H_{18}O_2N_6S_2$	m-CH_3	120	79
(VI h)	$C_{18}H_{16}O_2N_6S_2$	-H	182	85

All the compounds gave satisfactory C, H, N analysis.

Progress of the reaction and purity of the compounds was checked by TLC on silica gel-G coated glass plates using iodine vapour as visualizing agent. IR spectra was recorded on Shimadzu FTIR-8400S spectrophotometer and ^{1}H NMR spectra on in Gemini 200 MHz using TMS as an internal standard (Chemical shifts are expressed in δ ppm). The physical data are given in Table 1.

Table 2. Anti-bacterial activity

Compound	Zone of inhibition (in mm)			
	S. aureus		***E. coli***	
	50 mcg / mL	**100 mcg/ mL**	**50 mcg/mL**	**100 mcg/mL**
(VI a)	10	12	09	12
(VI b)	09	13	13	17
(VI c)	13	14	13	17
(VI d)	13	14	12	15
(VI e)	11	13	13	16
(VI f)	14	16	11	15
(VI g)	10	13	14	17
(VI h)	09	10	13	15
Std. I	21	24	-	-
Std. II	-	-	19	23

Std. I : Procaine penicillin; Std. II : Streptomycin

Table 3. Antifungal activity

Compound	Zone of inhibition (in mm)			
	C. albicans		***A. flavus***	
	50 mcg / mL	**100 mcg/ mL**	**50 mcg/mL**	**100 mcg/mL**
(VI a)	09	10	10	11
(VI b)	17	18	15	16

Cont…

Compound	Zone of inhibition (in mm)			
	C. albicans		*A. flavus*	
	50 mcg / mL	**100 mcg/ mL**	**50 mcg/mL**	**100 mcg/mL**
(VI c)	15	20	13	17
(VI d)	09	11	10	11
(VI e)	15	17	12	14
(VI f)	14	16	13	17
(VI g)	16	19	12	16
(VI h)	12	13	11	14
Std	17	20	18	21

Std : Griseofulvum

Synthesis of potassium dithiocarbazinates (IV a - h)

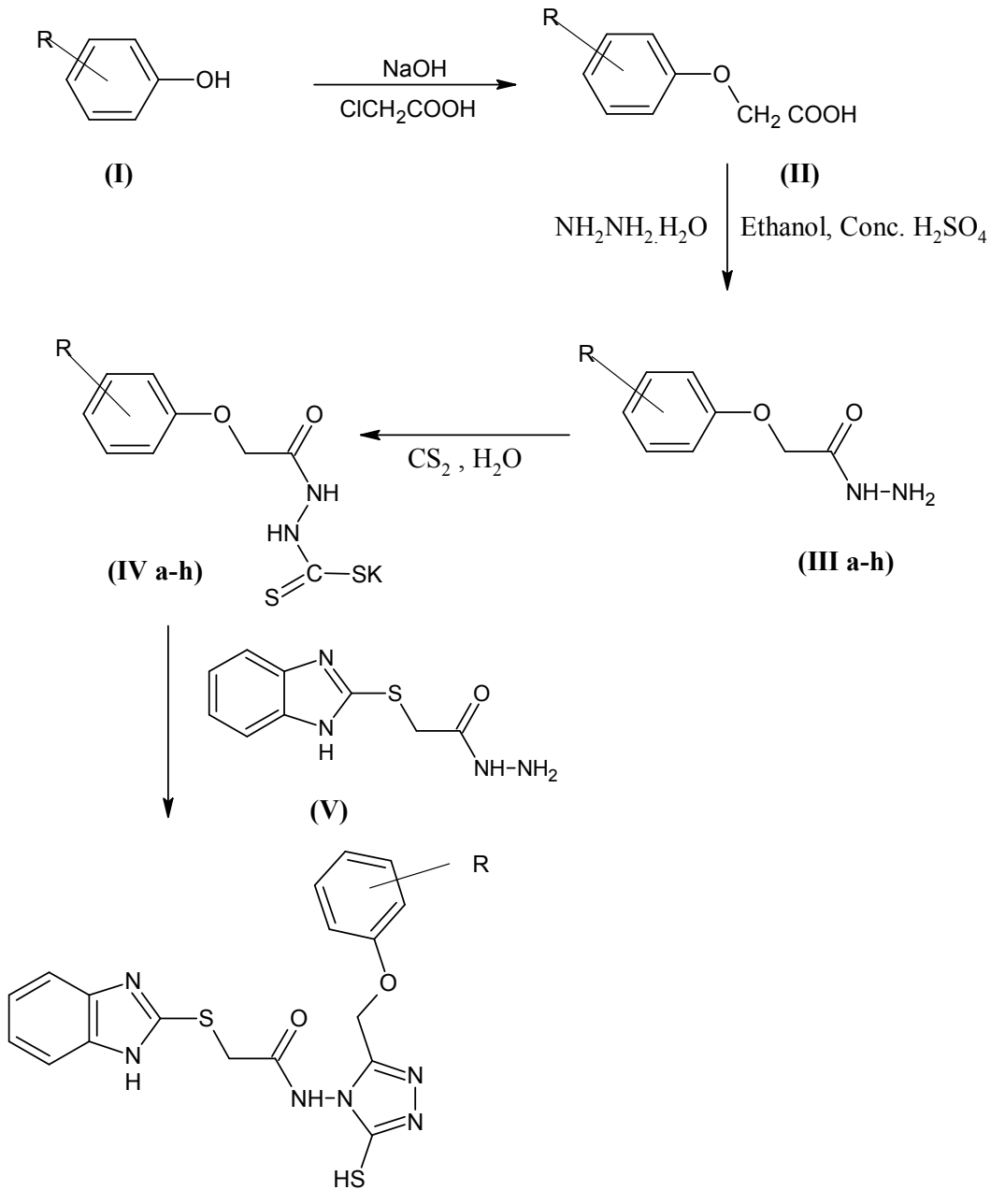
General procedure

Aryloxy acid hydrazides **(III a–h)**, 0.01 mol) and KOH (0.012 mol) in absolute alcohol (20 mL) was treated with CS_2 (0.015 mol) and the mixture was agitated for 8-10 hr and further diluted with ether (40 mL). The separated solid was filtered, washed with ether, dried and directly used for the next step without further purification.

Synthesis of 3-aryloxy methyl–4-[-2(benzimidazolyl thio) acetamide]-5-mercapto-1,2,4-triazoles (VI a–h)

General procedure

An equimolar mixture of aryloxy methyl potassium dithiocarbazinates **(IV a– h)**, 0.01 mol) and 2-(benzimidazolyl thio)- methyl acetic acid hydrazide **(V)** , (0.01 mol) were heated on oil bath at 160-170^0 C for 6-8 hr, till the evolution of hydrogen sulphide gas ceases. The reaction mixture was cooled and diluted with cold water. On careful acidification with dil. HCl, the solid separated was filtered, washed with cold water, dried and recrystalised from aqueous ethanol.


R
OH
NaOH
ClCH2COOH
R
O
CH2 COOH
(I)
(II)
NH2NH2.H2O
Ethanol, Conc. H2SO4
R
O
O
NH–NH2
(III a-h)
CS2 , H2O
R
O
O
NH
HN
C
SK
S
(IV a-h)
N
S
O
N
H
NH–NH2
(V)
R
O
N
S
O
N
H
NH–N
N
N
HS
(VI a-h)

Scheme

Spectral data

IR data in ($V_{max)}$ cm^{-1}, NMR in δ ppm.

(VI a): 3180-2890 (- NH), 1350 (C = S), 1670 (C = O), 1550 (C = N). NMR: 2.1 (d, 2H,OCH_2), 5.3 (d,2H, -SCH_2), 5.9 (s, 1H, NH), 7.0-7.45 (m, 8H, Ar-H), 9.2 (s, 1H, CONH). Peak for SH was not observed.

(VI c): 3190-2890 (- NH), 1340 (C = S) , 1630 (C = O) , 1530 (C = N). NMR: 1.8 (s, 3H, CH_3), 2.1 (d, 2H , OCH_2), 5.2 (d, 2H, SCH_2),5.5 (s, 1H, NH), 7.0-7.3 (m, 8 H, Ar-H), 9.5 (s, 1H , CONH), 12.5 (s, 1 H, SH).

(VI g): 3170-2850 (- NH), 1370 (C = S) , 1640 (C = O) , 1505 (C = N). NMR: 1.5 (s, 3H, CH3), 2.1 (d, 2H, OCH_2), 5.2 (d, 2H, SCH_2), 5.5 (s,1 H, NH) 7.0-7.4 (m, 8 H, Ar-H), 8.7. (s, 1H , CONH).

(VI h): 3140 (- NH), 1390 (C = S) , 1640 (C = O) ,1560 (C = N).NMR: 2.6 (d, 2H, OCH_2) 5.2 (d, 2H, SCH_2), 5.4 (s 1 H, NH) 7.0-7.4 (m, 9 H, Ar-H), 9.35. (s, 1H , CONH).

RESULTS AND DISCUSSION

In the present work, a series of novel 3-aryloxy methyl – 4-[2-(benzimidazolyl thio) acetamido]-5-mercapto-1, 2, 4-triazole**s** were synthesized. The structure of the synthesized compounds was confirmed on the basis of spectral data. All the newly synthesized compounds were evaluated for their antibacterial and antifungal activity. Amongst the compounds tested for antibacterial activity **(IIf)** showed moderate activity against gram + ve microorganism, whereas compounds **(IIb)**, **(IIc)** and **(IIg)** showed moderate activity against gram – ve pathogen. In the antifungal study **(IIc)** showed equipotent activity as that of standard at higher concentration (100 mcg / mL), whereas **(IIb)** and **(IIg)** showed moderate activity against *C. albicans*. Against the other tested organism that is *A. flavus* **(IIb)** and **(IIf)** showed moderate activity.

Antibacterial study of synthesized compounds reveals that none of the compound showed promising activity, only **(IIb)**, **(IIc)**, **(IIf)** and **(IIg)** showed moderate activity .Hence there is need for further structural modification to improve the efficacy of the compounds. Among compounds synthesized and tested for antifungal activity **(IIc)** is most potent as it is showing same degree of antifungal activity at 100 mcg / mL concentration as that of standard against *C. albicans*. Structure of the compound **(IIc)** reveals the presence of strong electron donating group –CH_3 in the structure. The other compound, which

showed moderate activity against *C. albicans* **(IIg)** also contain $-CH_3$ group. Hence it may be concluded that the presence of $-CH_3$ in the structure of titled compounds favored antifungal activity against *C. albicans*. However the results from antifungal activity against *A. niger* indicates **(IIb)** and **(IIg)** exhibited moderate activity. **(IIb)** contains electron withdrawing group $-NO_2$ group whereas **(IIg)** contains $-CH_3$ in the structure. This confirms that the $-CH_3$ group played vital role in antifungal activity of the synthesized compounds.

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REFERENCES

1. K. D. Tripati, Essentials of Medical Pharmacology, 5th Edition, Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, Anti-fungal Agents, p721.
2. Foye O. Willium and K. M. Varghese, Principles of Medicinal Chemistry, 2nd Edition, Company, Bombay, "Anti-anxiety agents", p 177.
3. U. S. Pathak, M. B. Devani, C. J. Shishoo and S. A. Shah, Indian J. Chem., **28B**, 83 (1989).
4. S. E. Abbas, H.E. Abou, G. M. El-Taliaw and A. B. Hasan, J. Egypt. Pharmceut. Sci., **32**, 503 (1991).
5. A. K. Dubey and N. K. Sangwan, Indian J. Hetero. Chem., **30**, 33 (1994).
6. S. N. Sawhney, Vir Dharam and Asha Gupta, Indian J. Chem., **29B**, 1107 (1990).
7. Kishan C. Joshi et al., Indian J. Chem., **28B** , 698 (1989).
8. V. K. Pandey, V. D. Gupta and D. N. Tiwari, Indian J. Hetero. Chem., **14,** 217 (2005).
9. G. M. Srinivasa, E. Jayachandran and B. Shivkumar, Indian J. Hetero. Chem., **14**, 65 (2004).
10. G. M. Srinivasa and B. Shivkumar, D. S. Rao and E. Jayachandran, Indian Drugs., **43(4**), 343 (2006).

11. Imhaz M. Hussain and Kumar Vinay, Indian J. Chem., **32(B),** 905 (1993).

12. S. Kakimoto and K. Yamamoto, J. Pharma. Soc., Japan, **74**, 997 (1954).

13. E. Jayachandran, L. V. G. Nargund, B. Shivkumar and Kamal Bhatia, Oriental J. Chem., **19(1)**, 139 (2003).

14. B. M. Gurupadaiah, E. Jayachandran, B. Shivkumar, A N. Nagappa and L. V. G. Nargund, Indian J. Hetero. Chem., **7**, 213 (1998).

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