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Research Article

SYNTHESIS OF SOME NOVEL 1, 3, 4 THIADIAZOLE CARRYING BENZIMIDAZOLE MOIETY AND THEIR ANTIMICROBIAL EVALUATION

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Abstract:

We have synthesized a series of α bromoketones& thiadiazole with various benzimidazoles. The compounds were confirmed by physical parameters (solubility, melting point), chromatographic methods (TLC) and at last spectroscopic methods (IR, NMR). Since our titled compounds are known to possess antimicrobial activity, the compounds were screened for their antibacterial and antifungal activity by cup-plate method. All the benzimidazole substituted thiadiazole derivatives (B1,B2,B and B4) showed significant activities compared to the standards ciprofloxacin for significant activity against *E.coli*,and*S.aureus*at 50, 100,300 and 500 mcg/ml and Miconazole significant activity against*Candida albicans*at 50, 100, 300,500 mcg/ml. The benzimidazole showed mild antibacterial activities and significant antifungal activities.

Keywords: α bromoketones, thiadiazole, benzimidazole & antimicrobial.

Introduction

Benzimidazole is a bicyclic compound having imidazole ring containing two nitrogen atoms at nonadjacent positions, fused to benzene. Benzimidazole is an important group of heterocyclicCompoundsthat are biologically active and of significant importance in medicinal chemistry[1]. A large number ofbenzimidazole derivatives have been found to exhibit various biological activities such as anti-inflammatory, antifungal[2,3], antibacterial and anthelmintic activities[4]. Benzimidazoles are present in various bioactive compounds having anticancer, anti- hypertension and antiviral properties[5] in addition being a component of Vitamin B_{12}[6].Similarly number of thiadiazole derivatives were also reported to possess varied biological activity such as bactericidal[7,8],,anti-inflammatory[9,] antitumor[10],fungicidal[11],

anticonvulsant, tuberculostatic, antithyrodial activities[12].Fascinated by varied various biological activity of benzimidazole and thiadiazole derivatives.it contemplated to synthesis new series 1, 3, 4 thiadiazole carrying benzimidazole moiety.

Materials and Methods

All chemicals used in the present investigation were of analytical grade.the synthesized compounds were purified by recrystallization method. The purity of the synthesized compounds was checked by TLC. The melting points of all the synthesized compounds were determined by open capillary method and are uncorrected.The molecular weight was determined by Mass spectra of the benzimidazole compounds were recorded using Micromass Quatto II triple quadrapole Mass Spectrometer SAIF Punjab University, Chandigarh. In the present investigation the IR spectra of benzimidazole compounds were recorded on Schimadzu FTIR spectrophotometer model 8400S in KBr pallets at Gurunanak college of pharmacy, Nagpur university, Nagpur, Maharashtra and the ^{1}H-NMR spectra of the benzimidazole compounds were recorded using BRUKER AVANCE II 400 Spectrometer SAIF Punjab University, Chandigarh DMSO as solvent and reported relative to TMS as internal standard. The 2-amino-5-benzylthio-1, 3, 4-thiadiazoles (II a-d) were synthesized from various 4-substituted bromo ketones (I a-d) and 2-amino-5-mercapto-1, 3, 4-thiadiazole.Diazotization of amines (II a-d) in conc. HCl in the presence of cu powder yielded 2-chloro-5-benzylthio-1, 3, 4–thiadiazole (III a-d).after that attachment with benzimidazole using dimethyl formamide(DMF) refluxed at 80 – 90^{0} C for 6 – 12 hrs.(IV a-d)

Experimental

Preparation of 5-benzylthio-2-amino-1, 3, 4-thiadiazoles (II a-d)

Addition of (0.1 mol) of 85% KOH to slurry of (0.1 mol) of 2-amino-1, 3, 4-thiadiazole -5- thiol in 10 ml of water produced brownish solution. This solution was clarified with activated charcoal and diluted with 28.5ml of ethanol. 0.1 mol. of various α-bromoketones were added rapidly with stirring. The thick reaction mixture formed was stirred for 30 min at room temperature, and then diluted with 200 ml of cold water. The solid obtained was removed by filtration, washed with water and ether. Crude products (**II a-d)** obtained were purified by recrystallization with aqueous ethanol to get colorless needles.

Preparation of 2-chloro-5-benzylthio-1, 3, 4-thiadiazole[13,14,]: (III a-d)

Compounds**(II a-d)**(10 mmol) was ground with an excess of sodium nitrite($NaNO_2$)(30 mmol) and the mixture was introduced in small portions and with stirring, into a ice cooled solution of 30 ml conc. HCl and 13 ml water, containing copper powder (0.1 times). The reaction mixture was allowed to stand at room temperature, and heated to 75 °C for 1 h. The reaction mixture was cooled and extracted with Chloroform ($CHCl_3$)(50ml x 3). The combined extracts were washed with sodium bicarbonate solution, dried over anhydrous sodium sulphate and chloroform was evaporated under reduced pressure to yield (**IIIa-d)**. The products were crystallized from ethanol.

1.1 General procedure for the synthesis of N-substituted benzimidazole[15] (IV a-d)

A mixture of equimolar quantities of compound **(III a-d)**, benzimidazole and $NaHCO_3$ in 5ml DMF was heated under reflux at 85-90°C for 12 h. After cooling 5ml of water was added to the reaction mixture and the precipitate was filtered, washed with water and crystallized from DMF-H_2O to give (50-60% w/w) of**(IV a-d)**

N-{2[1-(phenyl)-ethanon-2yl-sulfanyl]-1, 3, 4-thiadiazol-5yl} benzimidazole (IV a)

Yield 44 % w/w, amorphous, molecular weight 352.43, melting point 154-158 °C, IR (KBr) 697.87(C-S stretching), 1712.28 (C=O stretching), 1566.09 (C=N stretching), 3041.43 (Aromatic C-H stretching), 1554.52 (N-N stretching), Rf value, 0.51 (Chloroform: methanol, 9:1). Mass: molecular ion peak (M+) at m/z = 351.20, and; calculated for $C_{17}H_{12}N_4OS_2$ was 352.4. ^{1}H-NMR (TMS): 4.65 (s, C-H), 7.56- 7.91 (m, Ar-H f), 7.22-8.56 (m, Ar-H).

N-{2[1-(4-chloro-phenyl)-ethanon-2yl-sulfanyl]-1, 3, 4-thiadiazol-5yl} benzimidazole (IV b)

Yield 38 % w/w, amorphous, molecular weight 386.87., melting point 152-156 °C, IR (KBr) 690.47(C-S stretching), 1692.74 (C=O stretching), 1594.16 (C=N stretching), 3047.32 , 3060.82 (Aromatic C-H stretching), 1552.59 (N-N stretching), 750.4 (C-Cl stretching), Rf value, 0.62 (Chloroform: methanol, 9:1), Mass: molecular ion peak (M+) at m/z = 385.11, and calculated for $C_{17}H_{12}N_4OS_2Cl$ was 387.87, ^{1}H-NMR (TMS): 4.65 (s, C-H), 7.60-7.80 (m, Ar-H), 7.22-8.56 (m, Ar-H).

N-{2[1-(4-bromo-phenyl)-ethanon-2yl-sulfanyl]-1, 3, 4-thiadiazol-5yl} benzimidazole (IV c)

Yield 34 % w/w, amorphous, molecular weight 431.32, melting point 148-152 °C, IR (KBr) 723.07 (C-S stretching), 1704.96 (C=O stretching), 1618.17 (C=N stretching), 3001.03, 3027.44 (Aromatic C-H stretching), 1525.59 (N-N

stretching), 619.23 (C-Br stretching), Rf value, 0.67 (Chloroform: methanol, 9:1), Mass: molecular ion peak (M+) at m/z = 431.62, and calculated for $C_{17}H_{12}N_4OS_2Br$ was 431.32, ^{1}H-NMR (TMS): 4.65 (s, C-H), 7.71-7.95 (m, Ar-H), 7.22-8.56 (m, Ar-H).

N-{2[1-(4-nitro-phenyl)-ethanon-2yl-sulfanyl]-1, 3, 4-thiadiazol-5yl} benzimidazole (IV d)

Yield 42 % w/w, amorphous, molecular weight 397.43, melting point 156-160°C, IR (KBr) 697.87 (C-S stretching), 1712.28 (C=O stretching), 1566.09 (C=N stretching), 3041.43 (Aromatic C-H stretching), 1554.52 (N-N stretching), 1510.23 (C-NO_2 stretching), Rf value, 0.67 (Chloroform: methanol, 9:1), Mass: molecular ion peak (M+) at m/z =396.20, and calculated for $C_{17}H_{12}N_5O_3S_2$ was 397.43, ^{1}H-NMR (TMS): 4.65 (s, C-H), 8.31-8.37 (m, Ar-H), 7.22-8.56 (m, Ar-H).

Antimicrobial activity[16,17]

All the synthesized compounds were screened for their antibacterial activity against *E Coli, & S. aureus* by using disc diffusion method. Bacteria were cultured in nutrient agar medium and used as inoculum for study. The test compounds were dissolved in dimethyl sulfoxide (DMSO) to obtain a solution of 50,100,300,500µg/ml concentration. The compounds were also screened for their in vitro antifungal activities against *C.albicans.* The zones of inhibition of compounds for bacteria were compared with Ciprofloxacin and for fungi were compared with Miconazole. The zone of inhibition produced by test compounds was measured in mm. The data are given in Table-2.

Table- 1: Substituent's used for Synthesis of (Iv A-D)

Sr. No.	Compounds	R
1	**IV a**	H
2	**IV b**	Cl
3	**IV c**	Br
4	**IV d**	NO_2

Scheme

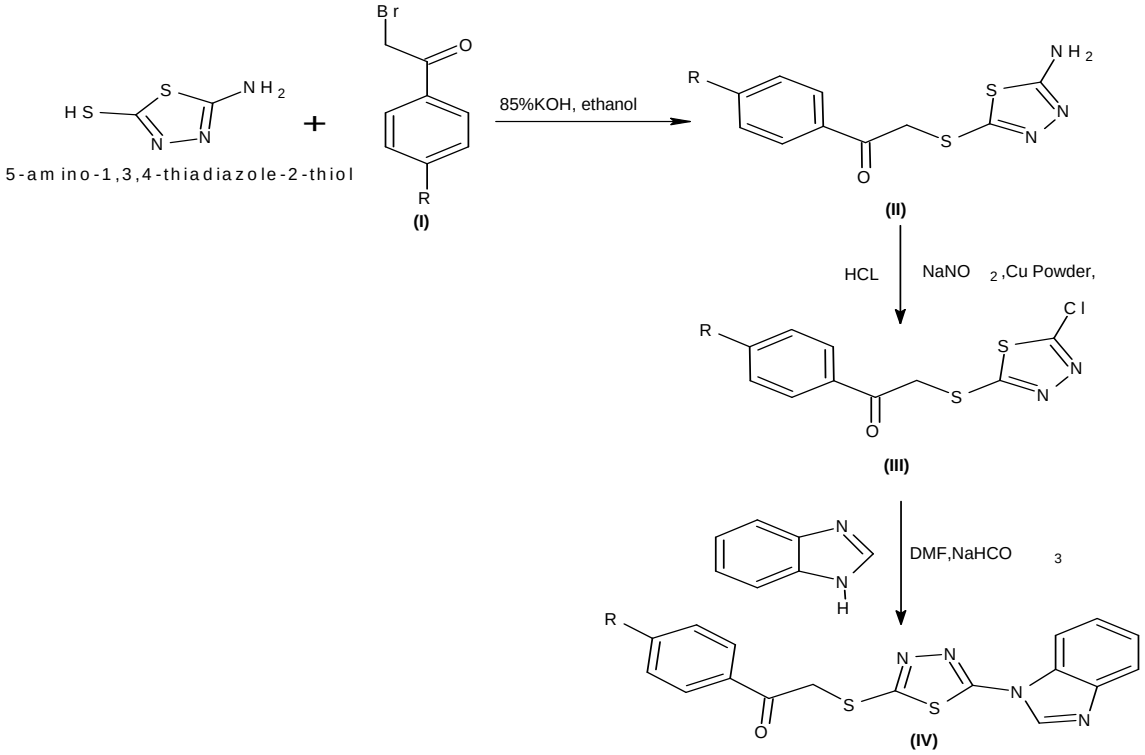

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Table-2: Physicochemical data of N-{2[1-(4-substituted phenyl)-ethanon-1yl-sulfanyl]-1, 3, 4-thiadiazol-5yl} benzimidazole (IV a-d).

Compound	R	m.p.(°C)	Yield (%w/w)	Nature	Molecular formula
IV a	H	154-158	44	Amorphous	$C_{17}H_{12}N_4OS_2$
IV b	Cl	152-156	38	Amorphous	$C_{17}H_{12}N_4OS_2Cl$
IV c	Br	148-152	34	Amorphous	$C_{17}H_{12}N_4OS_2Br$
IV d	NO_2	156-160	42	Amorphous	$C_{17}H_{12}N_5O_3S_2$

Table-3: Evaluation of Antimicrobial Activity of the Compounds.

	Compounds	**Zone of inhibition (mm)**			
		50µg/ml	**100µg/ml**	**300µg/ml**	**500µg/ml**
	IV a	**-**	**-**	**6**	**10**
E. coli	**IV b**	**-**	**7**	**12**	**15**

	IV c	**-**	**-**	**15**	**17**
	IV d	**7**	**11**	**13**	**16**
	Ciprofloxacin	**14**	**16**	**19**	**21**
S.aureus	**IV a**	**-**	**-**	**6**	**11**
	IV b	**-**	**7**	**11**	**14**
	IV c	**-**	**6**	**12**	**20**
	IV d	**11**	**13**	**16**	**19**
	Ciprofloxacin	**13**	**15**	**18**	**22**
C.*albicans*	**IV a**	**-**	**-**	**12**	**14**
	IV b	**-**	**12**	**14**	**16**
	IV c	**-**	**12**	**13**	**15**
	IV d	**12**	**14**	**15**	**17**
	Miconazole	**14**	**16**	**18**	**21**

Results and Discussion

The purity of the synthesized compounds was checked by performing thin layer chromatography and determining melting points. IR, Mass spectroscopy and 1HNMR spectra were consistent with the assigned structures. Since our titled compounds are known to possess antimicrobial activity, the compounds were screened for their antibacterial and antifungal activity by cup plate method.

Conclusion

In present investigation four benzimidazole derivatives have been successfully prepared. The derivatives are novel since nobody has attempted for their synthesis until now. The physico-chemical studies have revealed that the compounds are pure and having sufficient yield. The compounds were evaluated for their antimicrobial activities. Ciprofloxacin for bacteria and Miconazole for fungi were taken as standard antibiotic. From zones of inhibition it can concluded that all compound possess appreciable antibacterial and antifungal activities. Out of N-{2[1-(4-nitro phenyl)-

ethanon-2yl-sulfanyl]-1, 3, 4-thiadiazol-5yl} benzimidazole **IV d** was found to be good active against gram positive, gram negative and fungus (C.*albicans*)

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References

1. Devender P., Siddiqui N and Ahsan W., Benzimidazoles: A New Profile of Biological Activities Scholars Research Library Der Pharmacia Lettre, 2010, 2(2): pp27-34
2. Guven O., Erdogan T., Goekar H., and Yildiz S.,Bioorg Med Chem Lett,17,2007,pp2233
3. Kilciqil A.,and Altanlar N.,Turk J. chem,30,2006,pp223
4. Gowda J., Khadar A., KumariN.,andKallurayaB.,Microwave assisted synthesis of 1,3,4 oxadiazole carrying benzimidazole moiety Indian journal of chemistry 49B, 2010, pp1130-1134.
5. Horton A.; Bourne T.; SinytheL.*Chem. Rev*. 2003, pp*103*, 893
6. Mukhopadhyay C., Ghosh S., and Ray J.An efficient and versatile synthesis of 2, 2'-(alkanediyl)-bis-1*H*-benzimidazoles employing aqueous fluoroboric acid as catalyst: Density Functional Theory calculations and fluorescence studies ARKIVOC 2010 (ix) pp75-96
7. Abd E Rahman, A. H.; Ismail E. M. Arzneim.-Forsch/Drug Res. 1976, 26, pp756.
8. Dogan, H. N.; Buyuktimkin, S.; Rollas, S.; Yemni, E.; Cevikbas, A. Farmaco 1997, 52, pp565.
9. Atta, S. M. Sh.; Ammen, A. Arzneim.-Forsch./Drug Res. 1993, 43, 1354.
10. Dhapalapur, M. G.; Sabnis, S. S.; Deliwala, C. V. J. Med. Chem. 1968,pp11, 1014.
11. Foroumadi, F.; Daneshtalab, M.; Shafiee, A. Arzneim.-Forsch./Drug Res.1999, 49, pp1035.
12. Solak N and Rollas S Synthesis and antituberculosis activity of 2-(aryl/alkylamino)-5-(4- aminophenyl)-1,3,4-thiadiazoles and their Schiff basesARKIVOC 2006 (xii) pp173-181.

13. Poorrrajab F., Ardestani S., Emami S., Fardmoghadam M., Shafiee A. and Foroumadi A. Synthesis Nitroimidazolyl-1,3,4-thiadiazole-based anti-leishmanial agents and in-vitro biological evaluation European Journal of Medicinal Chemistry 44 (2009) pp1758–1762.
14. Foroumadi A., Emami S., Shafiee A., Pournourmohammadi S., and kharazmi A. synthesis and in vitro leishmanicidal activity of 2-(1-methyl-5-nitro-1H-imidazole-2yl)-5- substituted-1,3,4-thiadiazole derivatives European Journal of Medicinal Chemistry 40 (2005) pp1346–1350.
15. Foroumadi A., soltani F., Moshafi M., and Askari R. Synthesis and in vitro antibacterial activity of some N-(5-aryl-1, 3, 4-thiadiazole-2-yl) piperazinyl quinolone derivatives IL Farmaco 58 (2003) pp1023-1028.
16. Tayade G., *Asian Journal of Chemistry*, 2007, 19 (1), pp444-448.
17. Roche, Reverse Transcriptase Assay Colorimetric, Roche Diagnostics GmbH, 68298, Mannheim, Germany.