ISSN: 0975-766X
CODEN: IJPTFI
Available Online through
www.ijptonline.com
Research Article

SYNTHESIS AND EVALUATION OF SOME NOVEL 2-AMINO 1, 3, 4 THIADIAZOLE DERIVATIVES FOR THEIR ANTIMICROBIAL ACTIVITY

Kumud Mendhe*, Shekhar Waikar, Gulshan Gurunani.
Department of Pharmaceutical Chemistry, Gurunanak of College of Pharmacy,
Nagpur-440 026, Maharashtra, India.
Email: kumud.mendhe123@gmail.com

Received on 07-07-2012 *Accepted on 19-07-2012*

Abstract:

We have synthesized a series of α bromoketones & thiadiazole derivative. 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 substituted thiadiazole derivatives (IIa,IIb,IIc and IId) 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 2-amino1,3,4-thiadiazole dervatives showed mild antibacterial activities and significant antifungal activities.

Keywords: α bromoketones, thiadiazole & antimicrobial

Introduction

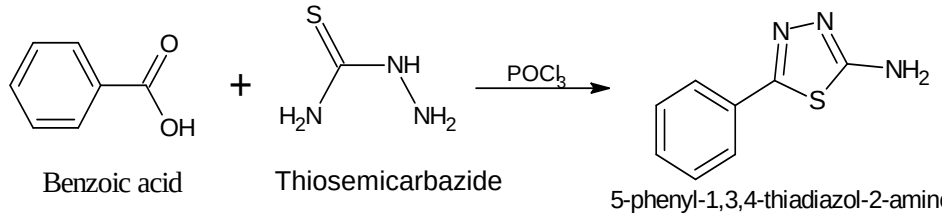
There are number of thiadiazoles which contain the nitrogen in different positions such as 1,2,3-thiadiazoles (**1**) and their benzo derivatives (**2**), the 1,2,4-thiadiazoles (**3**), the 1,3,4-thiadiazoles (**4**) and the 1,2,5-thiadiazles (**5**) and their benzo derivatives (**6**) etc. The basic ring 1,3,4-thiadiazole are fused heterocyclic ring compound having many biological activities such as antimicrobials[1,2] ,anti-inflammatory[3] ,anti-fungal[4], antibiotic, diuretic, antidepressant , anticancer[5] , anticonvulsants[6,7] , etc. Some examples showing prominent activities are acetazolamide (diuretic), sulfamethiazole (antibacterial), ceftazolene (antibiotic), atibeprone (antidepresant) etc.Thus 1,3,4-thiadiazole derivatives are compounds of deep interest because of their broad antibacterial spectrum to both Gram positive and Gram-negative bacteria and their good *in-vivo* chemotherapeutic efficacy.

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 thiadiazole compounds were recorded using Micromass Quatto II triple quadrapole Mass Spectrometer SAIF Punjab University, Chandigarh. In the present investigation the IR spectra of thiadiazole 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-phenyl -1, 3, 4-thiadiazoles (III a-d) were synthesized from various 4-substituted bromo ketones (I a-d) in the presence of potassium hydroxide.

Experimental

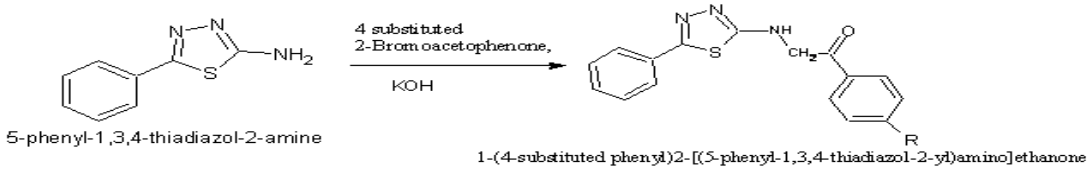
1. Preparation of 2-amino-5-(phenyl) -1,3,4-thiadiazole I [8,9].



Benzoic acid Thiosemicarbazide 5-phenyl-1,3,4-thiadiazol-2-amine

A mixture of the benzoic acid (10mmol),thiosemicarbazide (0.91g,10mmol) and phosphorus oxychloride(5ml) was gentely refluxed for 3hrs.After cooling, water(25ml) was added slowly and the reaction mixture was refluxed for 3hrs and filtered.The solution was neutralized with concentrated potassium hydroxide solution and the precipitate was filtered and recrystallized from ethanol m.p.220-222°C.(82%w/w).The physicochemical data is shown in Table no.1 .

2. Preparation of 1-(4-substituted phenyl) 2-[(5-phenyl-1,3,4-thiadiazol-2-yl)amino]ethanone[11].



5-phenyl-1,3,4-thiadiazol-2-amine

1-(4-substituted phenyl)2-[(5-phenyl-1,3,4-thiadiazol-2-yl)amino]ethanone

Addition of (0.1 mol) of 85% KOH to slurry of (0.1 mol) of 2-amino-5-(phenyl)1,3,4-thiadiazole **I** in 10 ml of water produced a 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 of **IIa-d** obtained were purified by recrystallization by aqueous ethanol to get colorless needles. The physicochemical data is shown in Table no. 2.

1-phenyl-2-[(5-phenyl-1,3,4-thiadiazol-2-yl)amino]ethanone (IIa)

Yield 38 % w/w, amorphous, molecular weight 295.35, melting point 175 °C, IR (KBr) 681.22 (C-S stretching), 1738.04 (C=O stretching), 1654.55 (C=N stretching), 3055.40 (Aromatic C-H stretching), 13480.44 (N-H stretching), Rf value, 0.79 (Benzene: methanol, 85:15). Mass: molecular ion peak (M+) at m/z =294.22, and; calculated for $C_{16}H_{13}N_3OS$was 295.31 .^{1}H-NMR (TMS): 4.56 (s,C-H), 4.12 (s, N-H), 7.49- 8.25 (m, Ar-H).

1-(4-chlorophenyl)-2-[(5-phenyl-1,3,4-thiadiazol-2-yl)amino]ethanone (II b)

Yield 43 % w/w, amorphous, molecular weight 329.80., melting point 182 °C, IR (KBr) 678.37 (C-S stretching), 1726.24 (C=O stretching), 1649.45 (C=N stretching), 3039.98 (Aromatic C-H stretching), 3438.25 (N-H stretching), 750 (C-Cl stretching), Rf value, 0.85 (Benzene : methanol, 85:15), Mass: molecular ion peak (M+) at m/z = 328.96, and calculated for $C_{16}H_{12}ClN_3OS$ was 329.80, ^{1}H-NMR (TMS): 4.69. (s, C-H), 4.098 (s,N-H)7.024-8.843 (m, Ar-H).

1-(4-bromophenyl)-2-[(5-phenyl-1,3,4-thiadiazol-2-yl)amino]ethanone (II c)

Yield 36 % w/w, amorphous, molecular weight 374.25, melting point 178 °C, IR (KBr) 650.12 (C-S stretching), 1700.28 (C=O stretching), 1653.36 (C=N stretching), 3046.66 (Aromatic C-H stretching), 3339.56 (N-H stretching), 500.00 (C-Br stretching), Rf value, 0.82 (Benzene : methanol, 9:1), Mass: molecular ion peak (M+) at m/z = 374.32, and calculated for $C_{16}H_{12}N_4OS$ was 374.25, ^{1}H-NMR (TMS): 4.57 (s, C-H), 3.93 (s,N-H)7.124-7.881 (m, Ar-H) .

1-(4-nitrophenyl)-2-[(5-phenyl-1,3,4-thiadiazol-2-yl)amino]ethanone (II d)

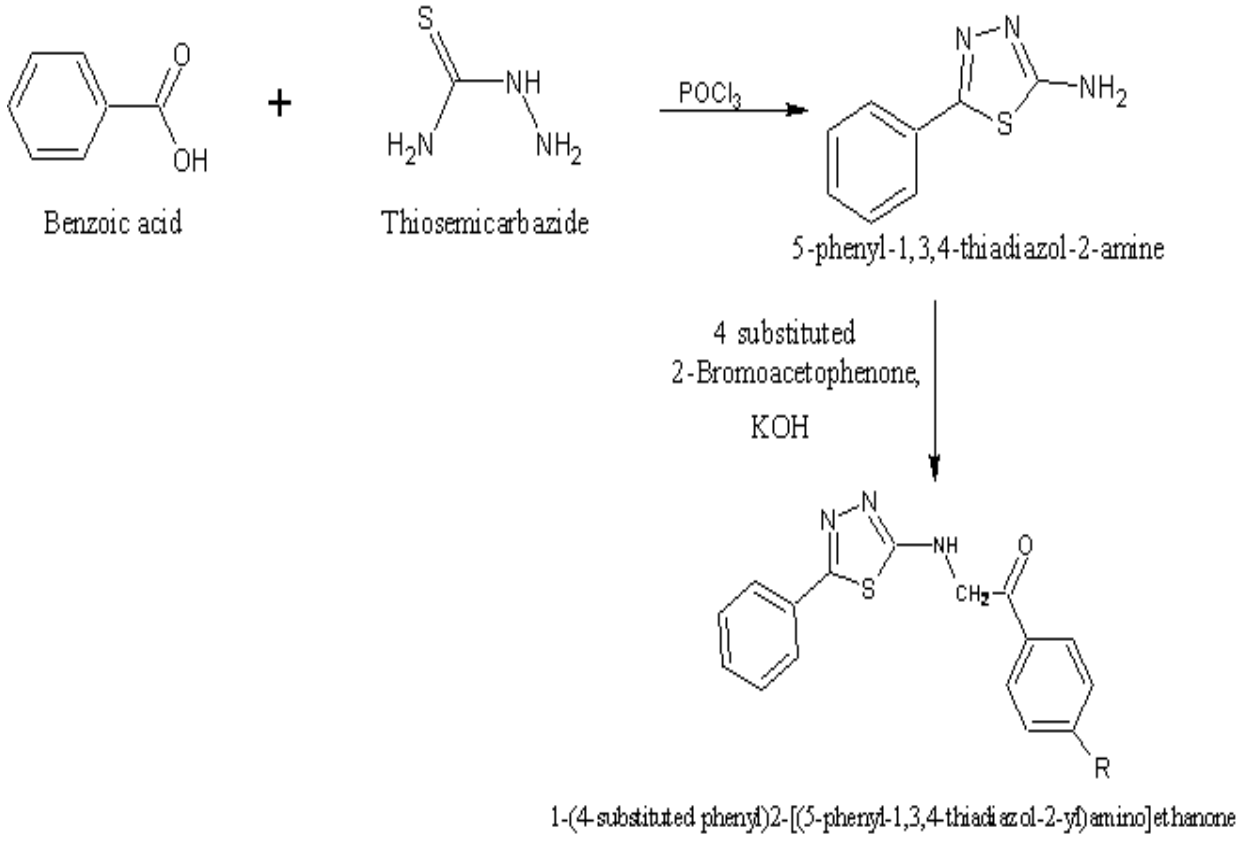
Yield 22 % w/w, amorphous, molecular weight 340.35, melting point 180°C, IR (KBr) 698.27 (C-S stretching), 1683.66 (C=O stretching), 1598.82 (C=N stretching), 3088.96 (Aromatic C-H stretching), 3272.39 (N-H stretching), 1500.00 (C-NO_2 stretching), Rf value, 0.86 (Benzene: methanol, 85:15), Mass: molecular ion peak

(M+) at m/z =340.57, and calculated for $C_{16}H_{12}N_4O_3S$ was 340.35, ^{1}H-NMR (TMS): 4.53(s, C-H), 3.89(s,N-H) , 7.144-8.501 (m, Ar-H).

Antimicrobial activity[12,13].

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-3.

Scheme



SCHEME FOR SYNTHESIS OF 2-AMINO 1, 3, 4-THIADIAZOLE DERIVATIVES

Substituent Used For Synthesis of (II a-d)

Compounds	R
IIIa	H
IIIb	Cl
IIIc	Br
IIId	NO_2

Table No. 1. Physicochemical data of 2-amino-5-(phenyl)1,3,4-thiadiazole-I.

Compound	m.p.(^{0}C)	Yield (%)	Nature	Molecular formula	Solubility
II	220-222	66	Amorphous	$C_8H_7N_3S$	Acetone

Table No. 2. Physicochemical data of 1-(4-substituted phenyl) 2-[(5-phenyl-1,3,4-thiadiazol-2-yl) amino]ethanone II a-d

Compound	R	M.P. (^{o}C)	Yield (%)	Nature	Molecular formula	Solubility
IIIa	H	175	38	Amorphous	$C_{16}H_{13}N_3OS$	Methanol
IIIb	Cl	182	43	Amorphous	$C_{16}H_{12}ClN_3OS$	Methanol
IIIc	Br	178	36	Amorphous	$C_{16}H_{12}BrN_3OS$	Methanol
IIId	NO_2	180	22	Amorphous	$C_{16}H_{12}N_4O_3S$	Methanol

Table 1 Evaluation of Antimicrobial Activity of the Compounds

	Compounds	Zone of inhibition (mm)			
		50µg/ ml	100µg/ml	300µg/ml	500µg/ml
E. coli	**IIIa**	14	18	24	36
	IIIb	17	30	35	36
	IIIc	10	12	14	35
	IIId	12	18	22	30

	Std.Ciprofloxacin	13	16	24	31
S.aureus	**IIIa**	15	19	25	35
	IIIb	-	-	26	35
	IIIc	-	-	12	17
	IIId	-	-	17	28
	Std.Ciprofloxacin	13	16	24	31
C.*albicans*	**IIIa**	-	19	25	33
	IIIb	20	15	18	26
	IIIc	14	9	21	24
	IIId	-	11	14	20
	Std.-Miconazole	14	19	24	27

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 thiadiazole 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. Compound **III d 1-(4-nitrophenyl)-2-[(5-phenyl-1, 3, 4-thiadiazol-2-yl) amino] ethanone** was found to be good active against gram positive, gram negative and fungus (C. *albicans*).

Acknowledgements

The authors are very thankful to Dr. A.M. Ittadwar Principal, Gurunanak of College of Pharmacy, Nagpur & the management for providing the facilities to carry out the work.

References:

1. Hussain S., Sharma J. andMohd. Amir Synthesis,antimicrobial activity of 1,2,4-triazole and 1,3,4-thiadiazole derivatives of 5-amino,2-hydroxybenzoic acid. European Journal of Chemistry. (2008); 5(4) : 963-968.
2. Patel D. and Singh A. Synthesis, Characterization and Antimicrobial activity of metal chelates of 5-[4-chlorophenyl (1,3,4)thiadiazol-2-ylaminomethylene]-8-hydroxy quinoline . Eur- Jour.Chem. 2009; 6(4):1017-22.
3. Burbuliene M. M. , Sakociute V. and Vanilavicius P. Synthesis and Characterization of new pyrimidine- based 1,3,4-oxa(thiadiazoles ,1,2,4-triazoles and 4-thiazolidinones and evaluated for anti-inflammatory activity . ARKIVOC, (2009); 12: 281-89.
4. Gupta S.K., Sharma P.K., Bansal M., and Kumar B. Synthesis and antifungal activity of 5-(o-Hydroxyphenyl)-2-[4'aryl-3'chloro-2; azetidinin-1-yl]-1,3,4-thiadiazole.Eur-J Chem. (2011); 8(2): 594-597.
5. Foroumadi A. , Asadipour A., Mirzaei M. , Karimi J. and Emami S. Synthesis ,evaluation of in vitro antituberculosis and cytotoxic activity of some 2-(5-nitro-2-furfuryl) 1,3,4-thiadiaole derivatives. Farmaco. (2004); 57: 765-69.
6. Stilings M.R., Welbourn A.P. and Walter D.S. Synthesis and anticonvulsant activity of substituted 2-hydrazino-1,3,4-thiadiazole. J. Med. Chem. (1986); 10: 2280-2284.
7. Froumadi A. , Sheiani V. , Sakhteman A. , Rameshk M. , Abbasi M. , Farazifard r. , Tabatabai S.A. and Shafiee A. Synthesis and anticonvulsant activity of novel amino-5-[4-chloro-2-(2-chlorophenoxy)phenyl]-1,3,4-thiadiazole derivatives . DARU. (2007); 15 (2).
8. Mullick P. , Khan S.A., Verma S. and Alam O. Synthesis , Characterizazion and Antimicrobial activity of new thiadiazole derivatives. Bull. Korean Chem. Soc.(2010); 31: 2345.
9. Tomi I.H.R., Al-Daraji A.H.R. ,Al-Qaysi R.R.T., Hasson M.M. and Al-Dulaimy K.H.D. Synthesis Characterization and Biological activities of some azo derivatives of aminothiadiazole derived from nicotinic and isonicotinic acids. Arabian J. of Chem. (2010); 30:320.
10. Vogel's textbook of practical organic chemistry revised by Furniss B., Hannaford A., Smith P., and Tatchell A. 5th edition, :1052.
11. Richard W. Young, et al. J. Am. Chem. Soc., 1956; 4649.

12. Ananthanarayan R. and Panikar C.K. Textbook of Microbiology .Madras, Orient longman , 2nd ed.(1981); 1.

13. Pelzar M.J., Chan E.C.S. and King N.R. Microbiology Mcgraw hills 5th ed. (1986).

Corresponding Author:

Kumud Mendhe

Email: *kumud.mendhe123@gmail.com*