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RESEARCH ARTICLE

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME 1, 3- DIHETEROARYL SUBSTITUTED-PROPAN-1-ONE DERIVATIVES

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ABSTRACT

Six new mannich bases were synthesized by reaction between 6-substituted-2-amino-benzothiazole and 5-substituted-1-(1*H*-1,2,4-triazol-1-yl)-ethanone in presence of formaldehyde and conc. HCl. The synthesized compounds were characterized by IR and ^{1}H-NMR spectroscopy. All the synthesized compounds were screened for *in vitro* antimicrobial activity against the pathogens *S. aureus, B. subtilis, P. aeruginosa, E. coli, A. niger* and *C. albicans*. Few synthesized derivatives were found to exhibit good antimicrobial activity.

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KEY WORDS

2-aminobenzothiazole, mannich base, 1*H*-1,2,4-triazole, antimicrobial.

INTRODUCTION

Increasing bacterial resistance towards the existing antibacterial drugs including antibiotics is one of the major reasons for the search and development of newer molecules as potential antibacterial. The 6-substituted-2-aminobenzothiazoles[1-3] and 1*H*-1,2,4-triazole derivatives[4-8] are reported to possess good antimicrobial activities. The products of Mannich reactions are emerged as therapeutically important molecules and includes amodiaquin (antimalarial), levopropoxyphene (antitussive), Fluoxetine (antidepressant), ethacrynic acid (diuretic) and many more. With the above observations it was planned to carry out mannich reaction between 6-substituted-2-aminobenzothiazoles and 5-substituted-1-(1*H*-1,2,4-triazol-1-yl)-ethanone to result into mannich bases containing both the 2-aminobenzothiazole and 1*H*-1,2,4-triazole heterocycles linked through aminoalkyl chain. Presence of both of these heterocycles in a single molecule is assumed to enhance the antimicrobial activity of new derivatives.

MATERIAL AND METHODS

The melting points of the synthesized compounds were determined on open capillary tubes and are uncorrected. The purity and homogeneity of the synthesized compounds was routinely ascertained by TLC using Benzene: Methanol (50:50 v/v) as solvent system for compounds bearing alky substituents on triazole ring and Carbon tetrachloride: Methanol (50:50 v/v) for compounds bearing aryl substituents on triazole ring. The absorption maxima of the synthesized compounds were carried out in methanol (analytical grade, 1mg/100mL). The methanolic solutions of the synthesized compounds were scanned on Shimadzu UV 1700 spectrophotometer, Kyoto, Japan in the region 200-400 nm. The infra red absorption spectra of the synthesized compounds were recorded using KBr disc on FTIR 8010 Shimadzu model. The ^{1}H-NMR spectra of the synthesized compounds were recorded on Brucker Spectrospin DPX 300 spectrophotometer. The solutions of the test compounds were prepared in dimethyl sulfoxide DMSO-d_6. Tetra Methyl Silane (TMS) was used as internal standard. The antimicrobial activity was measured by cup plate method using Ciprofloxacin and Fluconazole as standard drugs during evolution of antibacterial and antifungal activity respectively.

RESULTS AND DISCUSSION

Synthetic Results:

General procedure for synthesis of 3-(6-substituted-benzothiazol-2-ylamino)-1-(1H-1,2,4-triazol-1-yl)-propan-1-one derivatives[9-12]:

Compounds 1(a-f) and 2a were synthesized as per the reported methods and were obtained as per the reported yields. The compounds 3(a-f) were synthesized by mannich reaction between 1(a-f) and 2a in presence of formalin and conc. HCl. For these, in general, 1.1 mol of 1(a-f), 1.0 mol of 2a and 1.8 mol of formaldehyde were used. All the components were dissolved in rectified spirit and conc.HCl was added slowly with stirring. These solutions were refluxed for about 3-5h. The resultant reaction mixtures were kept at 0^0C for about 24h. The precipitated products were

recrystallized from rectified spirit. All the synthesized compounds were subjected to characterization by various physical methods.

3a: 3-(benzothiazol-2-yl-amino)-1-(1H-1,2,4-triazol-1- yl)-propan-1-one

White crystals, Yield 3.91g (43%), melting range 164 -6^{0}C, R_f 0.62, λ_{max} 239.14nm (methanol), IR (KBr, V max, cm^{-1}): 3184 (NH), 3000 (-CH, Ar), 2675 (-CH_2-CH_2), 1618 (-C=O), 1236 (-C-N), ^{1}H-NMR (DMSO-*d*6, δ ppm): 2.19-2.29(t, 2H, CH_2, α to NH), 3.70-3.77 (t, 2H, CH_2, α to –C=O), 4.17 (s, 1H, NH), 7.60-7.70 (m, 4H, benzothiazole), 9.42 (s, 1H, C-3'), 10.05 (s, 1H, C-5')

3b: 3-(6-methyl-benzothiazol-2-yl-amino)-1-(1H-1,2,4-triazol-1-yl)-propan-1-one

White crystals, Yield 2.45g (25%), melting range 178 -9^{0}C, R_f 0.62, λ_{max} 234.5nm (methanol), IR (KBr, V max, cm^{-1}): 3370 (NH), 3057 (-CH, Ar), 2828 (-CH_2-CH_2), 1670 (-C=O), 1325 (-C-N), ^{1}H-NMR (DMSO-*d*6, δ ppm): 3.15 (s, 3H, C6-CH_3), 3.70-3.77 (t, 2H, CH_2, α to NH), 3.97-4.03 (t, 2H, CH_2, α to –C=O), 4.60 (s, 1H, NH), 7.62-7.77 (m, 3H, Benzothiazole), 9.39 (s, 1H, C-3'), 10.05 (s, 1H, C-5')

3c: 3-(6-methoxy-benzothiazol-2-yl-amino)-1-(5-substituted-1H-1,2,4-triazol-1-yl)-propan-1-one

White crystals, Yield 3.86g (46%), melting range 208 -10^{0}C, R_f 0.71, λ_{max} 222.6nm (methanol), IR (KBr, V max, cm^{-1}): 3208 (NH), 2961 (-CH, Ar), 2872 (-CH_2-CH_2), 1718 (-C=O), 1458 (-CH_3), 1324 (-C-N), 1093(-OCH_3), ^{1}H-NMR (DMSO-*d*6, δ ppm): 3.45-3.61 (t, 2H, CH_2, α to NH), 4.21-4.41 (t, 2H, CH_2, α to –C=O), 4.49 (s, 3H, C6-OCH_3), 4.54 (s, 1H, NH), 6.42-7.77 (m, 3H, Benzothiazole), 9.39 (s, 1H, C-3'), 10.05 (s, 1H, C-5')

3d: 3-(6-chloro-benzothiazol-2-yl-amino)-1-(1H-1,2,4-triazol-1-yl)-propan-1-one

White crystals, Yield 2.66g (32%), melting range 230 -32^{0}C, R_f 0.60, λ_{max} 247.7nm (methanol), IR (KBr, V max, cm^{-1}): 3368 (NH),3179 (-CH, Ar), 2963 (-CH_2-CH_2), 1718 (-C=O), 1284 (-C-N), 800 (C-Cl), ^{1}H-NMR (DMSO-*d*6, δ ppm): 3.45-3.61 (t, 2H, CH_2, α to NH), 4.21-4.41 (t, 2H, CH_2, α to –C=O), 4.54 (s, 1H, NH), 6.60-7.33 (m, 3H, Benzothiazole), 9.39 (s, 1H, C-3'), 10.05 (s, 1H, C-5')

3e: 3-(6-bromo-benzothiazol-2-yl-amino)-1-(1H-1,2,4-triazol-1-yl)-propan-1-one

Yellowish white crystals, Yield 2.17g (28%), melting range 224 -5^{0}C, R_f 0.82, λ_{max} 208.5nm (methanol), IR (KBr, V max, cm^{-1}): 3200 (NH),3100 (-CH, Ar), 2925 (-CH_2-CH_2), 1680 (-C=O), 1224 (-C-N), 620 (C-Br), ^{1}H-NMR (DMSO-*d*6, δ ppm): 3.70-3.77 (t, 2H, CH_2, α to NH), 3.97-4.03 (t, 2H, CH_2, α to –C=O), 4.60 (s, 1H, NH), 6.68-7.33 (m, 3H, Benzothiazole), 8.90 (s, 1H, C-3'), 9.39 (s, 1H, C-5')

3f: 3-(6-nitro-benzothiazol-2-yl-amino)-1-(1H-1,2,4-triazol-1-yl)-propan-1-one

Yellow crystals, Yield 2.85g (35%), melting range 264-5^{0}C, R_f 0.90, λ_{max} 205.67nm (methanol), IR (KBr, V max, cm^{-1}): 3200 (NH),3100 (-CH, Ar), 2916 (-CH_2-CH_2), 1650 (-C=O), 1560 (C-NO_2), 1224 (-C-N), ^{1}H-NMR (DMSO-*d*6, δ ppm): 3.70-3.77 (t, 2H, CH_2, α to NH), 3.97-4.03 (t, 2H, CH_2, α to –C=O), 4.60 (s, 1H, NH), 7.62-7.73 (m, 3H, Benzothiazole), 9.39 (s, 1H, C-3'), 10.05 (s, 1H, C-5')

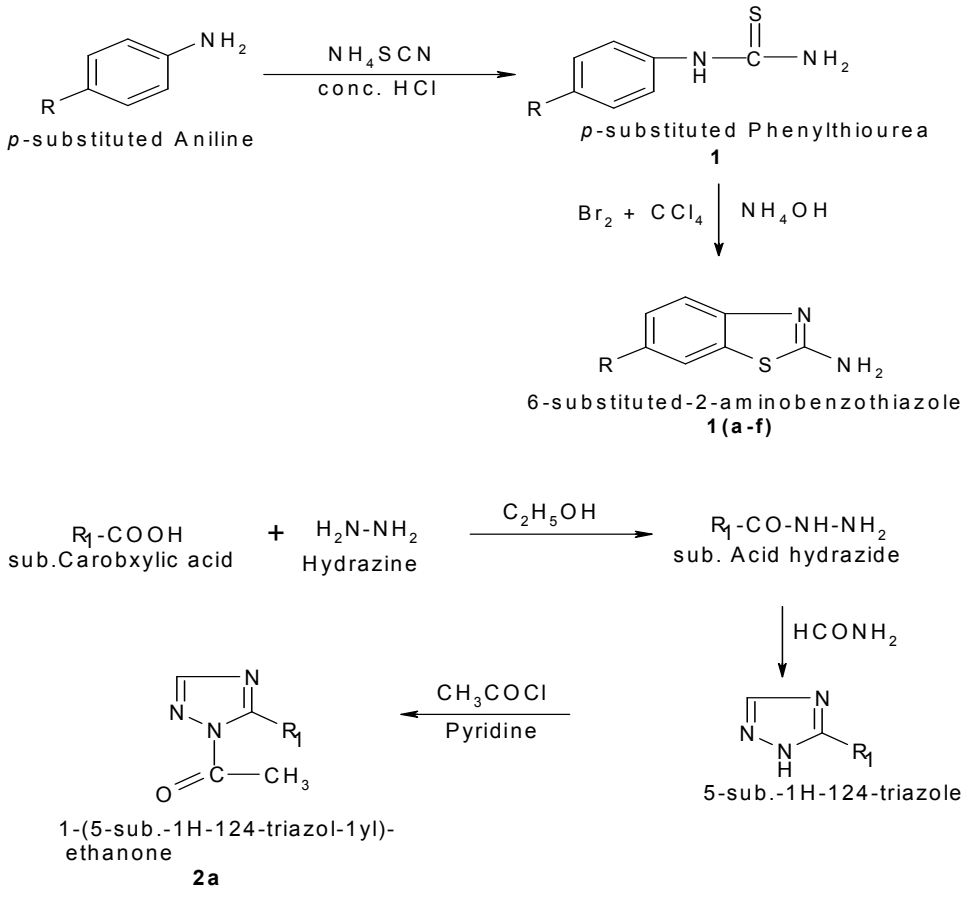
Antimicrobial activity[13-15]:

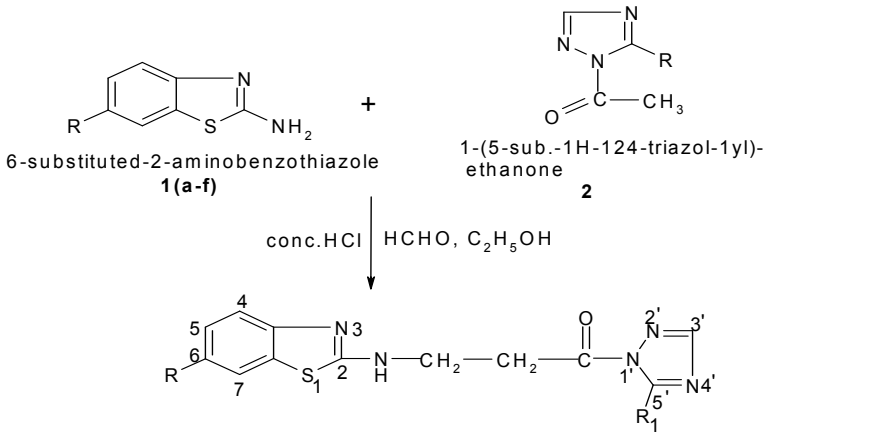
All the synthesized compounds i.e. 3(a-f) were screened for *in vitro* antimicrobial activity against four pathogenic bacteria viz. *S. aureus, B. subtilis, E. coli* and *P. aeruginosa* using Ciprofloxacin as the standard drug. The *in vitro* antifunal activity of the synthesized compounds was screened against the pathogenic fungi *A. niger* and *C. albicans* using Fluconazole as the standard drug. The solutions of the test and standard compounds were prepared in Dimethyl Formamide (DMF), the concentration of the prepared solutions being 100 µg/ml. The

results of antimicrobial activity are reported in Table 1 and 2.

Amongst the tested derivatives, 3a, 3d and 3f exhibited 85.71%, 125.00% and 86.95% activity against *S. aureus, C. albicans* and *B. subtilis* respectively. Thus it may be assumed that the antibacterial activity is greater for the derivatives having electron withdrawing substituents like $–NO_2$ on C-6 of benzothiazole ring. The antifungal activity was found to be related with the presence of powerful electron releasing groups like $–OCH_3$ on C-6 of benzothiazole ring. All the synthesized compounds exhibited moderate to excellent antimicrobial activity. Thus it is assumed that, more concentrated solutions of these derivates may have better activity.

Synthetic scheme





3-(6-substituted-benzothiazol-2-yl-amino)-1-(5-substituted-1H-1,2,4-triazol-1-yl)-propan-1-one
3(a-f)

R = -H, -CH_3, -OCH_3, -Cl, -Br, -NO_2
R_1= -H

Table 1
Results of in vitro antibacterial activity* of the synthesized compounds 3a-f.

Comp. no.	Gram +ve bacteria				Gram -ve bacteria			
	S. aureus		*B. subtilis*		*E. coli*		*P. aeruginosa*	
	ZOI (mm)	% Inhibition	ZOI (mm)	% Inhibition	ZOI (mm)	% Inhibition	ZOI (mm)	% Inhibition
3a	12	52.17	18	85.71	10	43.47	16	69.56
3b	04	17.39	12	57.14	06	26.08	14	60.86
3c	05	21.73	06	28.57	12	52.17	15	65.21
3d	13	56.52	06	28.57	08	34.78	05	21.73
3e	06	26.08	08	38.09	11	47.82	08	34.78
3f	07	30.43	08	38.09	20	86.95	09	39.13
Std.	23	100.00	21	100.00	23	100.00	23	100.00

Std.= Ciprofloxacin

Table 2
Results of in vitro antifungal activity* of the synthesized compounds 3a-f.

Comp. no.	*A. niger*		*C. albicans*	
	ZOI (mm)	% Inhibition	ZOI (mm)	% Inhibition
3a	13	68.42	05	31.25
3b	14	73.68	09	56.25
3c	10	52.63	04	25.00
3d	11	57.89	20	125.00
3e	10	52.63	07	43.75
3f	13	68.42	18	112.5
Std.	19	100.00	16	100.00

Std.= Fluconazole
** Diameter of zone of inhibition in mm. Control (DMF) = no activity. Both, test and standard compounds were tested at 100 µg/ml* ***ZOI(mm)=*** *Zone of inhibition in millimeter.*

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