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Short communication

Synthesis of some new 5-(2-substituted-1,3-thiazol-5-yl)-2-hydroxy benzamides and their 2-alkoxy derivatives as possible antifungal agents

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Abstract

The 2-hydroxy-5-(1,3-thiazol-5-yl) benzamide (**4a**), 5-(2-amino-1, 3-thiazol-5-yl)-2-hydroxy benzamide (**4b**), 2-hydroxy-5-(2-alkyl-1,3-Thiazol-5-yl) benzamide (**4c** and **4d**), 5-{2-[(N-substituted aryl)amino]-1,3-thiazol-5-yl}2-hydroxy benzamides (**6a–j**) were prepared by reacting 5-(bromoacetyl) salicylamide (**2**) with thiourea, thioformamide, thioalkylamide (**3c–d**) and substituted thioureas (**5a–j**) in absolute ethanol. These compounds were converted to 5-(2-substituted–1,3-thiazol-5-yl)-2-alkoxybenzamides and 5-(2-N-(substituted aryl)-1,3-thiazol-5-yl)-2-alkoxy benzamides (**8a–g**) by reacting with *n*-alkylbromides (**7a–b**) in presence of a base. The newly synthesized compounds were characterized by IR, ^{1}H-NMR and mass spectral data. Compounds were also screened for their antifungal activity.

Keywords: Antifungal studies; Thiazoles; Thioacetamide; Thiourea; Hydroxybenzamides

1. Introduction

Heterocycles containing thiazole ring system are found to exhibit wide spectrum of biological activities and many of them are well-known antiviral, antifungal agents and some are used as pesticides [1–6]. Imidacloprid isotere, a well-known insecticide possesses 2-chloro-5-substituted methylthiazole group [4].

Tripathy and Pradhan [7] have reported the preparation of *N*-thiazolyl and halothiazolyl amides of halogenated and non-halogenated salicylic and naphthoic acids and these compounds were tested for their antifungal activity against three phytopathogenic fungi of rice. One of the tested compound *N*-[4-(4-chlorophenyl)-2-thiazolyl] salicylamide effectively controlled *Helminthosporium oryza* and *Piricularia oryza* on rice.

Bayer et al. [8] reported the preparation of 2-thiazolyl-3-alkoxyacrylates and analogs as agricultural fungicides. The antibacterial activity of 7-(4-thiazolyl) quinolones and 7-(4-thiazidinyl) quinolones was discussed by Zhang et al. [9]. Some of the compounds showed good activity against Gram-positive bacteria and mycobacteria.

Prompted by these investigations, it was contemplated to synthesize some new 5-(2-substituted-1,3-thiazol-5-yl)-2-hydroxy benzamides, 5-{2-[(N-substituted aryl) amino]-1,3-thiazol-5-yl}-2-hydroxy benzamides and their 2-butoxy and 2-propyloxy derivatives and to investigate their antifungal activity.

2. Chemistry

Thioformamide, thioacetamide and thioisobutyramide were prepared by reacting corresponding amides with P_2S_5 in diethylether [10]. Substituted thioureas were synthesized by the reaction of benzoylchloride and ammonium thiocyanate with appropriate aniline by following standard literature procedure [11]. Treatment of thioamide/thiourea/-substituted thiourea with 5-(bromoacetyl) salicylamide gave 5-(2-(substituted)-1,3-thiazol-5-yl)-2-hydroxy benzamides (**4a–d**) and 5-{2-[(N-substituted aryl) amino]-1,3-thiazol-5-yl}-2-hydroxy benzamides (**6a–j**), (Schemes 1 and 2). 5-(Bromoacetyl) salicylamide was prepared by brominating

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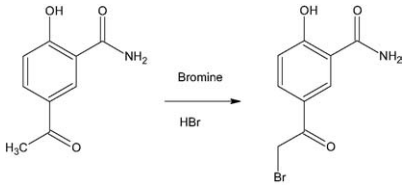
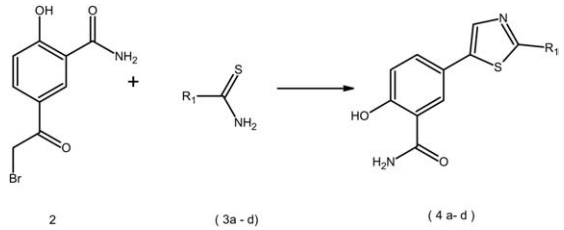


Scheme 1

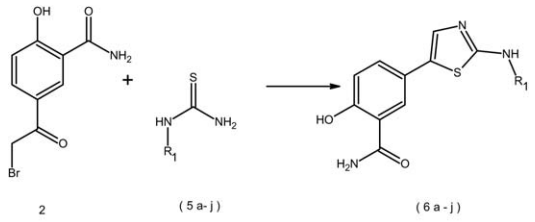


Compound No	R_1
3a, 4a	H
4a, 4b	NH_2
3c, 4c	CH_3
3d, 4d	$CH(CH_3)_2$

Scheme 2

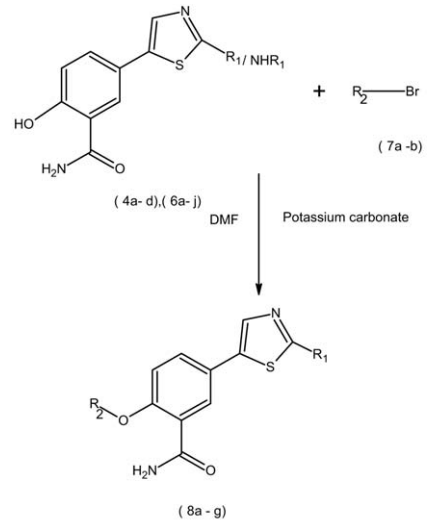
5-acetyl salicylamide (**1**) with bromine in ethyl acetate/ methanol media in presence of catalytic amount of hydrobromic acid, (Scheme 3) 5-(2-substituted-1,3-thiazol-5-yl)-2-alkoxy benzamides and 5-(2-*N*-(substituted aryl)-1,3-thiazol-5-yl)-2-alkoxy benzamides (**8a–g**) were obtained by treating 5-(2-substituted-1,3-thiazol-5-yl)-2-hydroxy benzamides (**4a–d**) and 5{-2-[(*N*-substituted aryl) amino]-1,3-thiazol-5-yl}-2-hydroxy benzamide (**6a–j**) with *N*-alkyl halides in DMF and potassium carbonate (Scheme 4).

The formation of thiazoles (**4a–d**), (**6a–j**) and their alkyl derivatives (**8a–g**) was confirmed by recording IR, ^{1}H-NMR and mass spectra of a few selected compounds. IR spectrum



Compound No	R_1
5a, 6a	$-C_6H_5$
5b, 6b	$-2-CH_3.C_6H_5$
5c, 6c	$-4-CH_3.C_6H_5$
5d, 6d	$-4-Br-C_6H_5$
5e, 6e	$-3-Cl-C_6H_5$
5f, 6f	$-4-Cl-C_6H_5$
5g, 6g	$-2-CF_3-C_6H_5$
5h, 6h	$-3Cl-4-CH_3.C_6H_5$
5i, 6i	$-2-C_5H_5N$
5j, 6j	$-6-CH_3-2-C_5H_3N$

Scheme 3



Compound No	R_1	R_2
8a	$-CH_3$	Propyl
8b	$-NH_2$	Propyl
8c	$-NHC_6H_5$	Propyl
8d	$-NH-4-CH_3-C_6H_5$	Propyl
8e	$-CH_3$	Butyl
8f	$-NHC_6H_5$	Butyl
8g	$-NH-3-Cl-C_6H_5$	Butyl

Scheme 4

of **4b** showed absorption band at 3407.9, 3188.1, 1670 and 1627, 1579 and 1251 cm^{-1} due to –OH, NH_2, $CONH_2$, C=N, C=S groups respectively. Mass spectra of the compounds **4b** and **4d** showed molecular ion peaks at *m/z* 234 (*I* = 80%) and *m/z* 262 (*I* = 20%) respectively, which is in agreement with their respective molecular formulae $C_{10}H_9N_3O_2S$ and $C_{13}H_{14}N_2O_2S$.

The ^{1}H-NMR spectrum of **6b** showed a sharp singlet at δ 2.39 corresponds to $-CH_3$ protons. A singlet at δ 6.61 corresponds to the NH proton. A multiplet in the region δ 7.35–7.40 and two doublets at δ 7.12–7.15 (J = 8.77) and δ 8.45–8.46 (J = 1.78) corresponds to the aromatic protons on benzene ring attached to –NH– group. A doublet of doublet at δ 7.7 is due to the protons on the benzene ring with hydroxyl and amide groups as substituents. Two singlets at δ 7.25 and δ 8.0 are due the coupling of two protons on amide NH_2 and a singlet at δ 9.68 due to the aromatic proton on thiazole ring. Mass spectra of **6b** showed molecular ion peak at *m/z* 325 (*I* = 40%), which is in agreement with its molecular formula $C_{17}H_{15}N_3O_2S$. IR spectrum of **6j** showed absorption bands at 3433, 3031, 1622, 1558 and 1446.5 and 1257.5 cm^{-1} due to –NH–, $-CH_3$, $CONH_2$, C=N, C=S groups, respectively.

^{1}H-NMR spectrum of the compound **8e** showed a sharp singlet at δ 2.77 is due to the $-CH_3$ group on thiazole ring and a singlet at δ 8.62 due to the aromatic proton on the thiazole ring. Two singlets at δ 5.89 and 7.87 are due to the $-NH_2$ protons of amide group. Two doublets in the range of δ 7.02–7.04 (J = 8.68) and δ 8.08–8.12 (J = 9.12) and one

singlet at δ 7.35 are due to the aromatic protons on the benzene ring. Butyl group present as the side chain showed two triplets at δ 0.99–1.04 and δ 4.16–4.20, a sextet at δ 1.47–1.59 and a quintet at δ 1.83–1.93 accounting for four different types of proton on the alkyl chain. Mass spectrum of **8e** showed molecular ion peak at *m/z* 290 (24.4%) that is in accordance with its molecular formula $C_{15}H_{18}N_2O_2S$ and a base peak at *m/z* 217(100%) due to fragmentation of –O–butyl chain.

3. Antifungal studies

Newly prepared compounds (**4a–d**), (**6a–j**) and (**8a–g**) were screened for their antifungal activity against *Aspergilus flavus* (NCIM No. 524), *Aspergilus fumigatus* (NCIM No. 902), *Candida albicans* (NCIM No. 3100), *Penicillium marneffei* (recultured) and *Trichophyton mentagrophytes* (recultured) in DMSO by serial plate dilution method [12–13]. Sabourands agar media was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 ml) and adjusting the pH to 5.7. Normal saline was use to make a suspension of spores of fungal strain for lawning. A loopful of particular fungal strain was transferred to 3 ml saline to get a suspension of corresponding species. A 20 ml of agar media was poured in to each of the petridishes. Excess of suspension was decanted and the plates were dried by placing in an incubator at 37 °C for 1 h. Using an agar punch wells were made on these seeded agar plates and 10 μg/ml of the test compounds in DMSO were added in to each well labeled. A control was also prepared for the plates in the same way using solvent DMSO. The petridishes were prepared in triplicate and maintained at 37 °C for 3–4 days. Antifungal activity was determined by measuring the diameter of the inhibition zone. Activity of each compound was compared with amphotericin B as standard. The minimum inhibitory concentration (MIC) for the amphotericin B in DMSO was more than 1 μg/ml against the tested species.

All tested compounds showed moderate to good antifungal activity against all fungi tested. Among the tested compounds, the compound 5-[(2-(3-chlorophenyl)-1,3-thiazol-5-yl]-2-butoxy benzamide (**8g**) has emerged as most active against all tested microorganisms, whereas **6a**, 2-hydroxy-5-{2-[(phenyl) amino]-1,3-thiazol-5-yl} benzamide is found to be least active. The compound **8g** structurally resembles a known antifungal agent *N*-[4-(4-chlorophenyl)-2-thiazolyl salicylamide [7]. Hence we can conclude that the higher activity of compound **8g** may be attributed to *N*-(4-chorophenyl) moiety. The zone of inhibition of tested compounds is given in Table 1.

4. Experimental

TLC was run on a Merck silica gel 60 F_{254} coated aluminum plates and melting points were taken in open capillary tubes and are uncorrected. IR spectra in KBr pellets were recorded on Shimadzu-FTIR Infrared spectrophotometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ and in DMSO-d_6 on a Varian (300 MHz) spectrometer using TMS as internal standard and Mass spectra were recorded on a Vg-s-70 micro mass, mass spectrometer operating at 70 eV.

4.1. Preparation of 5-(Bromoacetyl) salicylamide (2)

Ethylacetate (150 ml) and HBr (1 ml) were taken in a 250 ml RBF fitted with a mechanical stirrer. Reaction mix-

Table 1
Antifungal screening data of the compounds (5-(2-(N-substituted aryl)-1,3-thiazol-5-yl)-2-hydroxybenzamides (**6a–j**), 5-(-2-substituted)-1,3-thiazol-5-yl)-2-alkoxybezamides and 5-(-2-(N-substituted aryl)-1,3-thiazol-5-yl)-2-alkoxybezamides (**8a–g**) at 10 μg/ml

Compound number	*A. Flavus*	*A. Fumigatus*	*P. marneffei*	*T. mentagrophytes*	*C. albicans*
4b	+++	–	++	+++	+++
4c	–	–	–	+++	+++
6a	–	–	–	–	+++
6b	–	–	–	+++	+++
6c	–	–	–	+++	+++
6d	–	–	–	+++	+++
6e	+++	+++	–	+++	+++
6f	–	+++	+++	+++	+++
6g	+++	++	–	+++	++
6h	+++	–	–	+++	++
6i	+++	–	–	+++	–
6j	++	+++	–	+++	–
8a	–	++	–	+++	+++
8b	+++	–	++	++	–
8c	++	+++	–	+++	–
8d	+++	–	++	–	+++
8e	+++	–	–	+++	–
8f	+++	–	+++	++	
8g	+++	+++	++	+++	+++

–, < 8 mm, no inhibition; ++, 10–15 mm, moderate inhibition; +++, 15–20 mm maximum inhibition.

ture was then cooled to 5–10 °C. A 120.5 g (0.669 mol) of bromine was then slowly added at 5–10 °C for 1 h. In another 500 ml RBF that is connected with a mechanical stirrer and thermometer 100 g (0.558 mol) of 5-acetyl salicylamide (**1**), in 800 ml of ethylacetate was taken and 1 ml of HBr was added. The reaction mixture was cooled to 5–10 °C and the above prepared brominating mixture was slowly added for a period of 6 h. Reaction mixture was stirred for additional 12 h. The precipitated solid was filtered and washed with water. Crude product was then recrystalised in ethylacetate/acetic acid mixture. The 5-(Bromoacetyl) salicylamide (**2**) was isolated as off-white powder with a yield of 100 g (69.4%) and mp = 208–210 °C.

IR (KBr, γ_{max} cm^{-1}): 3417 (OH), 3361 and 3300 (–NH_2), 1666.4 and 1624 ($CONH_2$), 1288.4 (C–O_{str}) and 586.3 (C–Br).

*4.2. General procedure for the synthesis thioformamide and thioalkylamides (**3a, 3c–d**)[10]*

To a cooled (0–5 °C) solution of formamide (3.05 ml, 0.076 mol) in 100 ml diethylether was added 8.9 g (0.019 mol) of phosphorus pentasulphide in small portions. The reaction mixture was allowed warm to ambient temperature, stirred for 2 h, filtered, and concentrated in vacuum to afford thioformamide as a yellow offensive smelling oil, which was used without purification. Yield = 3.8 g (80%).

Similarly prepared thioacetamide and 2-methylpropanethioamide by reacting corresponding alkyl amides (0.115 mol) in 400 ml diethyl ether with of phosphorus pentasulphide (0.0115 mol).

*4.3. General procedure for the synthesis of N-substituted thioureas (**5a–j**)[11]*

Benzoylchloride (0.01 mol) was added over 5 min to a freshly prepared solution of ammonium thiocyante (0.012 mol) in dry acetone and the mixture was heated under reflux for about 15 min. Heating was stopped and appropriate aniline in acetone was added over a period of 15 min. The mixture was heated under reflux for 30 min and then poured to crushed ice. The resulting solid was collected, washed with water, followed by cold mixture of water and methanol (1:1). Suitably substituted benzoyl thioureas were added to preheated solution of aqueous sodium hydroxide (5%) and stirred. The mixture was then poured in to crushed ice containing hydrochloric acid (5%). The benzoic acid separated was removed by treating the reaction mixture with sodium carbonate. The product was collected, washed with water and then dried.

*4.4. General procedure for the synthesis of 5-(2-substituted-1,3-thiazol-5-yl)-2-hydroxy benzamides (**4a–d**) and 5-(2-(*N*-substituted aryl)-1,3-thiazol-5-yl)-2-hydroxy benzamides (**6a–j**)*

The 5-(bromoacetyl) salicylamide (0.01 mol) and appropriate thioamide/alkylthiomide/thiourea/substituted thiourea (0.01 mol) in absolute ethanol was refluxed for 6 h and allowed to stand overnight. The solid separated on cooling was filtered and recrystalised in a mixture of ethanol and dimethylformamide mixture (5–10% of dimethylformamide in ethanol).

4a 2-Hydroxy-5-(1,3-thiazol-5-yl) benzamide; this compound was obtained as tan colored micro crystals in a yield of 36%, mp 206–210 °C (Dimethylformamide/ethanol); *Anal*. calculated for $C_{10}H_8N_2O_2S$: *N*, 12.72; found: *N*, 12.8.

4b 5-(2-amino-1, 3-thiazol-5-yl)-2-hydroxybenzamide; this compound was obtained as off-white microcrystals in a yield of 65%, mp 286–290 °C (Dimethylformamide/ethanol) IR: (KBr, γ_{max}, cm^{-1}) 3407.9 cm^{-1} (OH), 3188.1 cm^{-1} (–NH_2), 1670 and 1627 cm^{-1} ($CONH_2$), 1579 cm^{-1} (C=N) 1251 cm^{-1} (C=S). MS: *m/z* 234(M–1, *I* = 80%), 219.2 (M–NH_2, *I* = 100%), 132.2 (salicylamide cation, *I* = 60%), 104 (2-aminothiazolyl cation *I* = 10%); *Anal*. calculated for $C_{10}H_9N_3O_2S$: *N*, 17.87; found: *N*, 17.9.

4c 2-Hydroxy-5-(2-methyl-1, 3-thiazol-5-yl) benzamide; this compound was obtained as off-white micro crystals in a yield of 75%, mp 284–288 °C (Dimethylformamide/ethanol); *Anal*. calculated for $C_{11}H_{10}N_2O_2S$: *N*, 11.96; found: *N*, 12.05.

4d 2-Hydroxy-5-(2-isopropyl-1, 3-thiazol-5-yl) benzamide; this compound was obtained as yellow crystals in a yield of 46%, mp 178–182 °C (Dimethylformamide/ethanol); MS: *m/z* 262 (M^+, *I* = 20%), 245(M–OH, *I* = 30%), 169 (salicylamide cation, *I* = 30%) *Anal*. calculated for $C_{13}H_{14}N_2O_2S$: *N*, 10.68; found: *N*, 10.7.

6a 2-Hydroxy-5-{2-[(phenyl) amino]-1,3-thiazol-5-yl} benzamide; this compound was obtained as greenish-yellow crystals in a yield of 65%, mp 247–250 °C (Dimethyl formamide/ethanol); *Anal*. calculated for $C_{16}H_{13}N_3O_2S$: *N*, 13.5; found: *N*, 13.42.

6b 2-Hydroxy-5-{2-[(2-methylphenyl) amino]-1,3-thiazol-5-yl} benzamide; this compound was obtained as off-white powder in a yield of 62%, mp 256–260 °C (Dimethylformamide/ethanol); ^{1}H-NMR: δ 2.39(s, 3H, –CH_3), δ 6.61(s, 1H, –NH), δ 7.35–7.40 (m, Ar–H), δ 7.12–7.15 *J* = 8.77 (d, Ar–H), δ 8.45–8.46 *J* = 1.78 (d, 1H, Ar–H), δ 7.7 (dd, Ar–H containing hydroxyl and amide groups), δ 7.25 and δ 8.0 (two s, $CONH_2$), δ 9.68 (s, Thiazole–H); MS: *m/z* 325 (M^+, *I* = 45%), 308 (M–OH, *I* = 35%), 281(M–$CONH_2$, *I* = 10%); *Anal*. calculated for $C_{17}H_{15}N_3O_2S$: *N*, 12.92; found: *N*, 12.76.

6c 2-Hydroxy-5-{2-[(4-methylphenyl) amino]-1,3-thiazol-5-yl} benzamide; this compound was obtained as white micro crystals in a yield of 61%, mp 230–234 °C (Dimethylformamide/ethanol); *Anal*. calculated for $C_{17}H_{15}N_3O_2S$: *N*, 12.92; found: *N*, 12.56.

6d 2-Hydroxy-5-{2-[(4-bromophenyl) amino]-1,3-thiazol-5-yl} benzamide; this compound was obtained as yellow crystals in a yield of 63%, mp 248–252 °C (Dimethylformamide/ethanol); ^{1}H-NMR: δ 6.72 (s, 1H, –NH–), δ 7.12–7.14, *J* = 8.74 (d, 1H, Ar–H), δ 7.29 (t, 1H,

Ar–H), δ 7.38 (t, 1H, Ar–H), δ 7.53 *J* = 6.20 (d, 1H, Ar–H), δ 7.55 (s, 1H, Ar–H) δ 7.93 (s, 1H $CONH_2$), δ 8.21 (s, Ar–H, Thiazole–H) *Anal*. calculated for $C_{16}H_{12}BrN_3O_2S$: *N*, 10.76; found: *N*, 10.67.

6e 2-Hydroxy-5-{2-[(3-chlrophenyl) amino]-1,3-thiazol-5-yl} benzamide; this compound was obtained as brownish-yellow crystals in a yield of 52%, mp 272–274 °C (Dimethyl formamide/ethanol); *Anal*. calculated for $C_{16}H_{12}ClN_3O_2S$: *N*, 12.15; found: *N*, 12.13.

6f 2-Hydroxy-5-{2-[(4-chlrophenyl) amino]-1,3-thiazol-5-yl} benzamide; this compound was obtained as light-yellow crystals in a yield of 49%, mp 268–272 °C (Dimethyl-formamide/ethanol); MS: *m/z* 345 (M^+, *I* = 20%), 330 (M–NH_2, *I* = 10%), 328 (M–OH, *I* = 25%); *Anal*. calculated for $C_{16}H_{12}ClN_3O_2S$: *N*, 12.15; found: *N*, 12.04.

6g 2-Hydroxy-5-{2-[(2-(trifluoromethyl) phenyl) amino]-1,3-thiazol-5-yl} benzamide: this compound was obtained as brownish yellow crystals in a yield of 55%, mp 178–182 °C (Dimethylformamide/ethanol); ^{1}H-NMR: δ 6.66 (s, 1H, NH), δ 7.16 *J* = 8.79 (d, 1H, Ar–H), δ 7.6 (s, 1H, Ar–H), 7.57 (s, 1H, –$CONH_2$), δ 7.97 (s, 1H, CONH2), δ 7.6 (dd, 2H, Ar–H), δ 7.63 (t, 1H, Ar–H), 7.76 (t, 1H, –Ar–H), δ 7.86 *J* = 7.68 (d, 1H, Ar–H), δ 7.71 *J* = 10.40 (d, 1H, Ar–H), δ 8.25 (s, 1H, thiazole–H); MS: *m/z* 341(M–F_2, *I* = 10%); *Anal*. calculated for $C_{17}H_{12}F_3N_3O_2S$: *N*, 11.08; found: *N*, 11.01.

6h 5-{2-[(3-Chloro-4-methylphenyl) amino]-1,3-thiazol-5-yl}-2-hydroxybenzamide: this compound was obtained as off-white plates in a yield of 62%, mp > 300 °C (Dimethyl-formamide/ethanol); *Anal*. calculated for $C_{17}H_{14}ClN_3O_2S$: *N*, 11.68; found: *N*, 11.52.

6i 2-Hydroxy-5-[2-(pyridin-2-ylamino)-1,3-thiazol-5-yl] benzamide: this compound was obtained as light-yellow powder in a yield of 57%, mp > 300 °C (Dimethyl-formamide/ethanol), MS: *m/z* 312 (M^+, 75%), 295 (M–OH, 100%), 267 (M–$CONH_2$); *Anal*. calculated for $C_{15}H_{12}N_4O_2S$: *N*, 17.94; found: *N*, 17.46.

6j 2-Hydroxy-5-{2-[(6-methylpyridin-2-yl)amino]-1,3-thiazol-5-yl}benzamide: this compound was obtained as light-yellow powder in a yield of 68%, mp > 300 °C (Dimethylformamide/ethanol); IR: (KBr, γ_{max}, cm^{-1}): 3433.1 (–NH–), 3031.9 (–CH_3), 1622 and 1558.4 ($CONH_2$), 1446 (C=C), 1336 (C=N), 1257.5 (C=S); *Anal*. calculated for $C_{16}H_{14}N_4O_2S$: *N*, 17.17; found: *N*, 17.02.

4.5. General procedure for the preparation of 5-(2-substituted-1,3-thiazol-5-yl)-2-alkoxy benzamides 5-(2-(N-substituted aryl)-1,3-thiazol-5yl)-2-alkoxy benzamides (8a–g)

The 5-(2-substituted-1,3-thiazol-5-yl)-2-hydroxy benzamide (0.01 mol), *n*-alkyl bromide (**7a–b**), (0.012 mol) and anhydrous potassium carbonate (0.015 mol) were taken in dry DMF and heated to 60 °C and maintained for 6–7 h under stirring. Reaction was monitored by TLC. After the completion of the reaction the reaction mixture was poured in 100 ml DM water and the precipitated product was filtered. Crude product was recrystallised from dimethylformamide–ethanol mixture. In the similar way converted 5-(2-(N-substituted aryl)-1,3-thiazol-5-yl)-2-hydroxy benzamides to corresponding 2-alkoxy derivative.

8a 5-(2-Methyl-1, 3-thiazol-5-yl)-2-propoxybenzamide; this compound was obtained as yellow micro crystals in a yield of 90%, mp 180–182 °C (Dimethylformamide/ethanol); ^{1}H-NMR: (DMSO-d_6), δ 1.10(t, 3H, –CH_3), δ 1.92 (sextet, 2H, –CH_2–), δ 2.76 (s, 3H, –CH_3), δ 7.87 (t, 2H, –CH_2), δ 5.97 (s, 1H, $CONH_2$), δ 7.03 (*J* = 8.72) (d, 1H, Ar–H), δ 7.3 (s, 1H, thiazole-H), δ 7.88 (s, 1H, $CONH_2$), δ 8.08 (dd, 1H, Ar–H), δ 8.63 (*J* = 2.32) (d, 1H, Ar–H), MS: *m/z* 276 (M^+, *I* = 25%), 217 (M–o–propyl, *I* = 100%); *Anal*. calculated for $C_{14}H_{16}N_2O_2S$: *N*, 10.14; found: *N*, 10.05.

8b 5-(2-Amino-1, 3-thiazol-5-yl)-2-propoxybenzamide; this compound was obtained as yellow micro crystals in a yield of 92%, mp 210–212 °C (Dimethylformamide/ethanol); *Anal*. calculated for $C_{13}H_{15}N_3O_2S$: *N*, 15.16; found: *N*, 15.03.

8c 5-(2-Anilino-1, 3-thiazol-5-yl)-2-propoxybenzamide; this compound was obtained as white crystals in a yield of 95%, mp 245–248 °C (Dimethylformamide/ethanol); *Anal*. calculated for $C_{19}H_{19}N_3O_2S$: *N*, 11.89; found: *N*, 11.78.

8d 5-{2-[(4-Methylphenyl) amino]-1,3-thiazol-5-yl}-2-propoxybenzamide; this compound was obtained as light pink micro crystals in a yield of 94%, mp 202–205 °C (Dimethylformamide/ethanol); *Anal*. calculated for $C_{20}H_{21}N_3O_2S$: *N*, 11.44; found: *N*, 11.49.

8e 2-Butoxy-5-(2-methyl-1,3-thiazol-5-yl)benzamide: this compound was obtained as light-yellow microcrystals in a yield of 94%, mp 148–150 °C (Dimethylformamide/ethanol); ^{1}H-NMR: (DMSO-d_6), δ 2.77 (s, thiazole –CH_3), δ 8.62 (thiazole–H), δ 5.89 and 7.87 (two s, –NH_2 of amide group), δ 7.02 *J* = 8.68 (d, 1H, Ar–H) and δ 8.12 (dd, 2H, Ar–H), δ 7.35 (s, thiazole-H), [δ 0.99–1.04 (t), δ 4.16–4.20(t), at δ 1.47–1.59 (sextet) and δ 1.83–1.93 (quintet)-butyl side chain], MS: *m/z* 290(M^+, *I* = 28%), 217 (M–O–butyl, *I* = 100%); *Anal*. calculated for $C_{15}H_{18}N_2O_2S$: *N*, 9.65; found: *N*, 9.64.

8f 5-(2-Anilino-1,3-thiazol-5-yl)-2-butoxybenzamide: this compound was obtained as white crystals in a yield of 92%, mp 248–250 °C (Dimethyl formamide/ethanol); IR (KBr, γ_{max}, cm^{-1}): 3462 (OH), 3300 (NH), 2929 and 2871.8 (C–H_{str}), 1666.4 (–$CONH_2$), 1593.1 and 1562 (NH_{def}), 1271 (C–O_{str}), 1163 (C=N) and 1082 (C=S), δ 0.98 (t, 3H, –CH_3), ^{1}H-NMR: (DMSO-d_6); δ 1.42–1.55 (quintet, 2H, –CH_2–), δ 1.75–1.88 (sextet, 2H, –CH_2–), δ 4.05–4.01 (t, 2H, –CH_2), δ 5.94 (s, 1H, $CONH_2$), δ 6.73 (s, 1H, thiazole–H), δ 6.76–6.79 (*J* = 8.7) (d, 1H, Ar–H), δ 7.07 (dd, 1H, Ar–H), δ 7.26–7.41 (m, 3H, Ar–H), δ 7.75 (s, NH, $CONH_2$), δ 8.08 (s, 1H, Ar–H), δ 8.19 (s, 1H, 1H, Ar–H); *Anal*. calculated for $C_{20}H_{20}N_3O_2S$: *N*, 11.47; found: *N*, 11.34.

8g 2-Butoxy-5-{2-[(3-chlorophenyl)amino]-1,3-thiazol-5-yl}benzamide: this compound was obtained as off-white powder in a yield of 93%, mp 198–202 °C (Dimethyl formamide/ethanol); *Anal*. calculated for $C_{20}H_{20}ClN_3O_2S$: *N*, 10.46; found: *N*, 10.39.

5. Conclusion

Generating compound libraries through synthesis is a tool to identify a pharmacophore. We have synthesized about 21 compounds containing thiazole ring system, which resemble a known antifungal agent *N*-[4-(4-chlorophenyl)-2-thiazolyl]-salicylamide. Among the tested compounds, the compound 5-[2-(*N*-3-chlorophenyl)-1,3-thiazol-5-yl]-2-butyloxybenzamide (**8g**) emerged as most active compound. Hence this study has widened the scope of developing thiazole derivatives as promising antifungal agents.

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