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# Microwave Assisted Synthesis and Antimicrobial Screening of 2-Aryl-5H-3-(3',5'-dichloro-2-benzo(b)thiophenoylamino)-4-thiazolidinones

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**The synthesis of some new potentially bioactive 4-thiazolidinone has been undertaken. The required 2-(substituted benzalhydrazinocarbonyl)-3,5-dichloro-benzo(b)thiophene(2) was prepared by reaction of 2-hydrazinocarbonyl-3,5-dichloro benzo(b)thiophene(1) with different aryl aldehyde. The compounds (2) on cyclocondensation with thioglycolic acid under micro wave irradiation as well as in a conventional way yielded the corresponding 4-thiazolidinones (3). The structures of synthesized compounds were deduced on the basis of their elemental analyses and spectral analyses (IR and $^1$H NMR). The synthesized compounds were evaluated for their antimicrobial activity.**

4-Thiazolidinones have been extensively explored for their wide biological and industrial applications[1-3]. A series of 2-Aryl-5H-3-(3',5'-dichloro-2-benzo(b)thiophenoylamino)-4-thiazolidinone (**3**) have been synthesized by cyclocondensation of 2-(substitutedbenzal hydrazinocarbonyl)-3,5-dichlorobenzo(b)thiophene (**2**) with thioglycolic acid under microwave irradiation as well as conventional heating. The schiff's bases (**2**) were prepared by reaction of 2-hydrazinocarbonyl-3,5-dichlorobenzo (b)thiophene (**1**) with different aryl aldehyde. The reaction time has been brought down from hours to minutes with improved yield using microwave irradiation (MWI).

Recently reported studies on the use of domestic microwave oven for the synthesis of heterocycles[4-7], showed that it is safe, rapid and convenient methodology, keeping in view the substantial reduction in the reaction time with improved yield, some new 4-thiazolidinone derivatives prepared under MWI using a domestic microwave oven as well as in a conventional way.

Melting points were taken in open capillary tubes and are uncorrected. IR spectra (KBr) ($cm^{-1}$) were recorded on a Shimadzu-8400 FTIR spectrophotometer and $^1$H NMR spectra were recorded on a Brucker spectrometer (300 MHz) using TMS as an internal standard (chemical shift in δ ppm). The purity of the compounds was checked on silica gel coated plates.

To synthesize 2-hydrazinocarbonyl-3,5-dichlorobenzo(b)thiophene (**1**) a solution of 3,5-dichlorobenzo (b)thiophene-2-carbonyl chloride (2.65 g, 0.01 mol) in ethanol and hydrazine hydrate (0.5 g, 0.01 mol) was refluxed on water bath for 5-6 h. The product was isolated and recrystallized from ethanol to give (1). Yield 68%, m.p. 212°. IR (KBr) ($cm^{-1}$): 3286 (NH-), 1624 (C=0), 796 (C-S-C), 777 (C-Cl). NMR (δppm): 8.3 (s,1H,-NH); 7.9 (s,1H,Ar-$H_1$); 7.65 (dd,1H,Ar-$H_2$); 7.45 (dd,1H,Ar-$H_3$).

*For correspondence

To synthesize 2-(Substituted benzalhydrazinocarbonyl)-3,5-dichloro-benzo(b)thiophene (2) a solution of 2-hydrazinocarbonyl-3,5-dichloro-benzo(b)thiophene (1) (2.61 g, 0.01 mol) and different aryl aldehyde (0.01 mol) in dioxane was refluxed for 5 h. The product was isolated and crystallized from suitable solvent to give (2a-l). Compound 2e: Yield 63%, m.p. 190°,. Anal.calcd. for $C_{17}H_{12}N_2O_3SCl_2$, Calcd. C,51.65; H,3.04; N,7.09%. Found C,51.62; H,3.02; N,7.07%. IR (KBr) ($cm^{-1}$): 3450 (-OH), 3303(NH-), 1627 (C=0), 781 (C-S-C), 752 (C-Cl). NMR (δppm): 8.6 (b,s,1H,-NH); 6.6-7.9 (7H,Ar-H); 3.95 (s,3H,-$OCH_3$). All the characteristic data and NMR spectral data of other compounds (2a-l) are given in Table 1 and Table 1(A), respectively.

To synthesize 2-Aryl-5H- 3-(3',5' dichloro-2'-benzo(b)thiophenoylamino)-4-thiazolidinones (3) a homogenous mixture of hydrazines (2a-l) (0.01 mol) and thioglycolic acid (0.92 ml, 0.01 mol) was taken in a conical flask capped with glass funnel and subjected to microwave irradiation for 6 min. The reaction mixture was cooled and triturated with

TABLE 1: PHYSICAL DATA OF COMPOUNDS 2a-l AND 3a-l.

| Compd. | R | M.P. (°) | Yield (%) | Mol. Formula | % of N Calcd. | % of N Found |
|---|---|---|---|---|---|---|
| 2a | -$C_6H_5$ | 200 | 68 | $C_{16}H_{10}N_2OSCl_2$ | 8.02 | 8.01 |
| 2b | 3,4-$(OCH_3)_2$, $C_6H_3$ | 260 | 64 | $C_{18}H_{14}N_2O_3SCl_2$ | 6.84 | 6.81 |
| 2c | 2-$C_4H_3O$ | 180 | 65 | $C_{14}H_8N_2O_2SCl_2$ | 8.26 | 8.24 |
| 2d | 4-OH, $C_6H_4$ | 110 | 69 | $C_{16}H_{10}N_2O_2SCl_2$ | 7.67 | 7.65 |
| 2e | 3-$OCH_3$,4-OH, $C_6H_3$ | 190 | 63 | $C_{17}H_{12}N_2O_3SCl_2$ | 7.09 | 7.07 |
| 2f | 4-N,N-$(CH_3)_2$- $C_6H_4$ | 120 | 68 | $C_{18}H_{15}N_3OSCl_2$ | 10.71 | 10.68 |
| 2g | 2-$NO_2$, $C_6H_4$ | 170 | 69 | $C_{16}H_{10}N_3O_3SCl_2$ | 10.66 | 10.65 |
| 2h | 3-$OC_6H_5$, $C_6H_4$ | 180 | 67 | $C_{22}H_{14}N_2O_2SCl_2$ | 6.35 | 6.33 |
| 2i | 4-S-$CH_3$, $C_6H_4$ | 195 | 61 | $C_{17}H_{12}N_2OS_2Cl_2$ | 7.09 | 7.08 |
| 2j | 3,4,5-$(OCH_3)_3$, $C_6H_2$ | 225 | 63 | $C_{19}H_{16}N_2O_4SCl_2$ | 6.38 | 6.34 |
| 2k | 3-[2-Cl,6-$OCH_3$-$C_9H_4N$] | >300 | 65 | $C_{20}H_{12}N_3O_2SCl_3$ | 9.04 | 9.02 |
| 2l | 3-[2-Cl,6-$CH_3$-$C_9H_4N$] | 205 | 66 | $C_{20}H_{12}N_3OSCl_3$ | 9.36 | 9.35 |
| 3a | -$C_6H_5$ | 235 | 68 | $C_{17}H_{12}N_2O_2S_2Cl_2$ | 6.81 | 6.80 |
| 3b | 3,4-$(OCH_3)_2$, $C_6H_3$ | >300 | 65 | $C_{19}H_{16}N_2O_4S_2Cl_2$ | 5.94 | 5.91 |
| 3c | 2-$C_4H_3O$ | 195(d) | 67 | $C_{15}H_{10}N_2O_3S_2Cl_2$ | 6.98 | 6.95 |
| 3d | 4-OH, $C_6H_4$ | 200 | 62 | $C_{17}H_{12}N_2O_3S_2Cl_2$ | 6.55 | 6.52 |
| 3e | 3-$OCH_3$,4-OH, $C_6H_3$ | 230(d) | 60 | $C_{19}H_{14}N_2O_3S_2Cl_2$ | 5.97 | 5.94 |
| 3f | 4-N,N-$(CH_3)_2$, $C_6H_4$ | 190 | 69 | $C_{19}H_{17}N_3O_2S_2Cl_2$ | 9.25 | 9.21 |
| 3g | 2-$NO_2$, $C_6H_4$ | 205 | 67 | $C_{17}H_{11}N_3O_4S_2Cl_2$ | 9.21 | 9.18 |
| 3h | 3-$OC_6H_5$, $C_6H_4$ | 246 | 62 | $C_{23}H_{16}N_2O_3S_2Cl_2$ | 5.56 | 5.54 |
| 3i | 4-S-$CH_3$, $C_6H_4$ | 160(d) | 61 | $C_{18}H_{14}N_2O_2S_3Cl_2$ | 6.12 | 6.09 |
| 3j | 3,4,5-$(OCH_3)_3$, $C_6H_2$ | 215 | 60 | $C_{21}H_{18}N_2O_5S_2Cl_2$ | 5.46 | 5.45 |
| 3k | 3-[2-Cl,6-$OCH_3$-$C_9H_4N$] | 210 | 63 | $C_{22}H_{15}N_3O_4S_2Cl_3$ | 7.56 | 7.55 |
| 3l | 3-[2-Cl,6-$CH_3$-$C_9H_4N$] | 215 | 63 | $C_{22}H_{15}N_3O_3S_2Cl_3$ | 7.78 | 7.75 |

sodium bicarbonate solution and isolated product recrystallized from suitable solvent to give (3a-l). Compound 3k: Yield 63%, m.p.210° ,. Anal.calcd. for $C_{22}H_{15}N_3O_4S_2Cl_3$, Calcd. C,47.52; H,2.70; N,7.56 %. Found C,47.50; H,2.67; N,7.53%. IR (KBr) ($cm^{-1}$): 3207 (NH-), 1733 (C=0, thiazolidinone), 1658 (C=O), 781 (C-S-C, thiazolidine ring), 750 (C-Cl), 713 (C-S-C). NMR (δppm): 8.6 (b,s,1H,-NH); 6.6-7.9 (m,7H,Ar-H); 5.59(s,1H,-CH); 4.1 (s,2H,-$CH_2$); 3.93 (s,3H,-$OCH_3$). All the characteristic data and NMR spectral data of other compounds (3a-l) are given in Table 1 and Table 1(A), respectively.

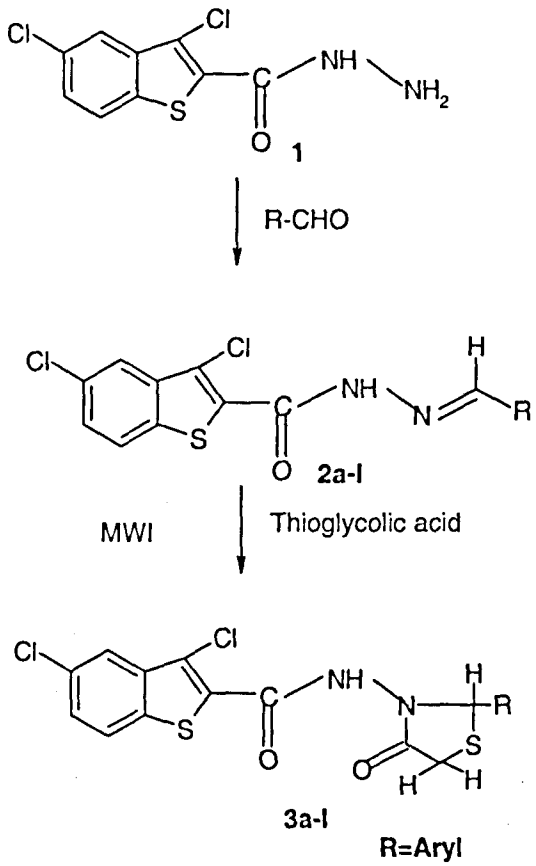
The antimicrobial activity was determined using agar cup-plate diffusion method[8] by measuring the inhibition zone in mm. All the compounds were screened *in vitro* for their antimicrobial activity against a variety of microbial strains such as *Escherichia coli, Proteus vulgaris, Bacillus megaterium, Staphylococcus aureus* and the fungal strain *Aspergillus niger*. Known antibiotics like ampicillin, amoxycillin, ciprofloxacin, erythromycin and griseofulvin

TABLE 1(A): NMR SPECTRAL STUDIES OF COMPOUNDS 2a-l AND 3a-l.

| Compd. | -$CH_2$ | -CH | -X | Ar-H | -NH |
|---|---|---|---|---|---|
| 2a | - | - | - | 6.6-7.9(m,8H) | 8.6(s,2H) |
| 2b | - | - | 3.95(s,3H,$OCH_3$) | 6.4-7.5(m,6H) | 8.5(s,2H) |
| 2c | - | - | - | 6.7-7.5 (m,6H) | 8.3(s,2H) |
| 2d | - | - | - | 6.7-7.8(m,7H) | 8.7(s,2H) |
| 2e | - | - | 3.90(s,3H,$OCH_3$) | 6.8-7.9 (m,6H) | 8.5(s,2H) |
| 2f | - | - | 1.45(s,3H,$CH_3$) | 6.5-7.8(m,7H) | 8.8(s,2H) |
| 2g | - | - | - | 6.4-7.5(m,7H) | 8.4(s,2H) |
| 2h | - | - | - | 6.4-7.5(m,7H) | 8.7(s,2H) |
| 2i | - | - | 1.46(s,3H,$CH_3$) | 6.6-7.9(m,7H) | 8.6(s,2H) |
| 2j | - | - | 3.89(s,3H,$OCH_3$) | 6.7-7.8(m,5H) | 8.3(s,2H) |
| 2k | - | - | 3.95(s,3H,$OCH_3$) | 6.6-7.9(m,7H) | 8.6(s,2H) |
| 2l | - | - | 1.47(s,3H,$CH_3$) | 6.4-7.9(m,7H) | 8.4(s,2H) |
| 3a | 3.73(s,2H) | 5.62(s,1H) | - | 6.4-7.5(m,8H) | 8.7(s,1H) |
| 3b | 3.72(s,2H) | 5.61(s,1H) | 3.93(s,3H,$OCH_3$) | 6.6-7.9(m,6H) | 8.6(s,1H) |
| 3c | 3.70(s,2H) | 5.60(s,1H) | - | 6.8-7.9(m,6H) | 8.8(s,1H) |
| 3d | 3.74(s,2H) | 5.62(s,1H) | - | 6.7-7.8(m,7H) | 8.9(s,1H) |
| 3e | 3.69(s,2H) | 5.59(s,1H) | 3.87(s,3H,$OCH_3$) | 6.6-7.9(m,6H) | 8.5(s,1H) |
| 3f | 3.71(s,2H) | 5.59(s,1H) | 1.43(s,3H,$CH_3$) | 6.7-7.8(m,7H) | 8.2(s,1H) |
| 3g | 3.74(s,2H) | 5.58(s,1H) | - | 6.4-7.5(m,7H) | 8.4(s,1H) |
| 3h | 3.73(s,2H) | 5.62(s,1H) | - | 6.4-7.5(m,7H) | 8.5(s,1H) |
| 3i | 3.68(s,2H) | 5.61(s,1H) | 1.45(s,3H,$CH_3$) | 6.7-7.8(m,7H) | 8.3(s,1H) |
| 3j | 3.75(s,2H) | 5.63(s,1H) | 3.85(s,3H,$OCH_3$) | 6.6-7.8(m,5H) | 8.7(s,1H) |
| 3k | 4.10(s,2H) | 5.59(s,1H) | 3.93(s,3H,$OCH_3$) | 6.6-7.9(m,7H) | 8.6(s,1H) |
| 3l | 3.68(s,2H) | 5.60(s,1H) | 1.47(s,3H,$CH_3$) | 6.4-7.5(m,7H) | 8.4(s,1H) |

TABLE 2: ANTIMICROBIAL SCREENING RESULTS OF COMPOUNDS 2a-l AND 3a-l.

| Compd. | Antimicrobial activity Zones of inhibition (mm) | | | Antifungal activity | |
|---|---|---|---|---|---|
| | *E. coli* | *P. vulgaris* | *B. megaterium* | *S. aureus* | *A. niger* |
| 2a | 15 | 16 | 14 | 17 | 12 |
| 2b | 17 | 17 | 21 | 13 | 19 |
| 2c | 15 | 15 | 15 | 15 | 12 |
| 2d | **21** | 14 | 12 | 16 | 15 |
| 2e | 14 | 16 | 15 | 16 | 15 |
| 2f | 12 | 15 | 17 | 13 | 16 |
| 2g | **23** | 14 | 13 | 17 | 23 |
| 2h | 16 | 14 | 19 | 14 | 17 |
| 2i | 17 | **18** | 14 | 14 | 13 |
| 2j | 16 | 13 | 12 | 15 | 12 |
| 2k | **22** | 16 | 15 | 21 | 14 |
| 2l | 13 | **20** | 17 | 14 | 13 |
| 3a | 14 | 13 | 16 | 15 | 17 |
| 3b | 16 | **18** | 17 | 12 | 16 |
| 3c | 12 | 14 | 15 | 17 | 15 |
| 3d | 16 | 12 | 15 | 15 | 15 |
| 3e | 15 | **20** | 17 | 16 | 13 |
| 3f | 14 | 17 | 13 | 14 | 15 |
| 3g | 16 | **18** | 14 | 12 | 12 |
| 3h | 17 | 16 | 14 | 13 | 14 |
| 3i | 15 | 14 | **22** | 16 | 20 |
| 3j | **22** | 15 | 15 | 17 | 14 |
| 3k | **18** | **23** | 13 | 15 | 22 |
| 3l | 17 | **18** | 16 | 19 | 15 |
| Ampicillin | 16 | 24 | 20 | 25 | 0 |
| Amoxycillin | 17 | 21 | 22 | 29 | 0 |
| Ciprofloxacin | 26 | 28 | 23 | 24 | 0 |
| Erythromycin | 22 | 18 | 10 | 22 | 0 |
| Griseofulvin | 0 | 0 | 0 | 0 | 21 |




**Synthesis of compounds 2a-l and 3a-l.**

**2a-l: (Substitutedbenzal hydrazine carbonyl)-3,5-dichloro benzo(b)thiophene. 3a-l: 2-Aryl-5H-(3',5'-dichloro-2-benzo(b)thiophenoylamino)-4-thiazolidinones.**

showed highest activity (15-18 mm) against these organisms. Compound 2d, 2g, 3j, 3k, exhibited significant activity against *E. coli,* respectively. In case of antifungal activity compound 2b, 2g, 3i, 3k were highly active against *A. niger* (Table 2).

All the compounds synthesised were evaluated for their *in vitro* antimicrobial activity against Gram +ve bacteria like *B. megaterium* and *S. aureus* and Gram –ve bacteria like *E. coli* and *P. Vulgaris*. The fungal strain used for testing was *A. niger*. The standard drugs used for comparison were ampicillin, ciprofloxacin, erythromycin and griseofulvin. Some compounds from the synthesised compounds displayed highest activity against above microbes. The other compounds show mild to moderate activity against these organisms. Table 2 represents the activity observed against the microbes investigated.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