Synthesis and Antimicrobial Activity of Bis[4-methoxy-3-(6-aryl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)phenyl]methanes and Bis[(triazolo[3,4-b]thiadiazepin-3-yl)phenyl]methanes

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Abstract

A series of novel bis[4-methoxy-3-(6-aryl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)phenyl]methanes and bis[(triazolo[3,4-b]thiadiazepin-3-yl)phenyl]methanes (5a–e and 6a–e) has been synthesized and characterized by IR, $^1$H and $^{13}$C NMR, MS and elemental analysis. All the newly synthesized compounds were screened for their antibacterial activity against Bacillus subtilis, Staphylococcus aureus, Klobsinella aerogenes and Chromobacterium violaceum and antifungal activity against Candida albicans, Aspergillus fumigatus, Trichophyton rubrum and Trichophyton mentagrophytes. Compounds 5b, 5d, 5e, 6b, 6c and 6e exhibited potent activity against the tested bacteria and fungi, and emerged as potential molecules for further development.

Keywords: Bis[4-methoxy-3-(6-aryl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)phenyl]methanes, bis[(triazolo[3,4-b]thiadiazepin-3-yl)phenyl]methanes, organic synthesis, antibacterial activity, antifungal activity.

1. Introduction

Heterocyclic compounds represent one of the most active classes of compounds possessing a wide spectrum of biological activities, including antibacterial, antifungal, and other biological activities.1–6 The biological activities of various 1,2,4-triazole derivatives and their N-bridged heterocyclic analogs have been widely investigated as antitumor,7 antiviral,8 anti-inflammatory,9 analgesic,10 and antidepressant.11 It is interesting to use 1,2,4-triazole derivatives as precursors in the synthesis of some important biologically active heterocycles,12–15 which constitute an important class of organic compounds with diverse biological activities, including antiparasitic, analgesic, antibacterial and anti-inflammatory activities.16–21 In addition, it was reported that triazole fused with a six-membered ring system is also found to possess diverse applications in the field of medicine.22–28 The commonly known systems are triazole-pyridines,26 triazole-pyridazines,27 triazole-pyrimidines,28 triazole-triazines,29 triazole-pyrazines,30 triazole-triazenes,31 a few monomeric triazole-thiadiazine,31 and triazole-thiadiazepines,32 although there are not many triazoles fused to thiadiazines and thiadiazepines, there is a number of them that are incorporated into a wide variety of therapeutically important compounds possessing a broad spectrum of biological activities.33–37

In recent years attention has been increasingly paid to the synthesis of bis-heterocyclic compounds which exhibit various biological activities,38–41 including antibacterial, fungicidal, tuberculostatic and plant-growth regulating properties. Further development during the recent years42 indicates that the bis-heterocyclic compounds display much better antibacterial activity than the monomeric counterparts.

Owing to the immense importance and varied bioactivities exhibited by triazolo-thiadiazines and thiadiazepines and in continuation of our work on biologically active heterocycles,43–51 we were stimulated to integrate thiadiazines moieties in a triazole framework, since these systems possess well documented antimicrobial activity. In this connection, some bis-heterocyclic compounds such as bis-triazolo thiadiazines and triazolo-thiadiazepines have been synthesized and evaluated for their antibacterial and antifungal activity. For the synthesis of target com-
pounds, 4-aminono1-1, 2, 4-triazol-3-thione is used as an intermediate because the amino and mercapto groups are appropriate nucleophile centers for the synthesis of fused heterocyclic compounds.

2. Results and Discussion

5,5’-Methylenebis(2-hydroxybenzoic acid) (2), required for the synthesis of the title compounds, was prepared according to the procedure described in the literature. Compound 2 on reaction with methyl iodide, in the presence of aq. KOH at 80 °C, furnished 5-(3-formyl-4-methoxybenzyl)-2-methoxybenzoic acid (3). The condensation of 3 with thiocarbohydrazide at melt temperature for 3 h afforded bis[4-methoxy-3-[4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl]phenyl]methane (4) as a yellow solid (Scheme 1). IR spectrum of 4 showed two absorption bands in the region of 3335–3235 and 2596 cm⁻¹ assigned to NH and SH groups, two absorption bands at 1554 and 1512 cm⁻¹ attributable to C=N vibrations, providing a strong evidence for the formation of a triazole ring. ¹H NMR spectrum of 4 showed two signals at δ 2.17 and 5.47 ppm corresponding to –SH and –NH₂ protons, respectively. The aromatic protons appeared in the δ 6.62–9.93 ppm in accord with the structure. ¹³C NMR spectrum of 4 showed signals at δ 156.6 and 134.4 ppm corresponding to the 3-C and 5-C of the triazole moiety, respectively. The other signals observed were at the expected chemical shifts with appropriate integrals. Elemental analyses are also consistent with the structures proposed for compounds 5a–e and 6a–e.

3. Antibacterial Evaluation

All the newly synthesized compounds 5a–e and 6a–e were screened for their antibacterial activity against Gram-positive bacteria viz. Bacillus subtilis (MTCC 441), Staphylococcus aureus (MTCC 96), and Gram-negative bacteria viz. Klebsiella aerogenes (MTCC 39) and Chromobacterium violaceum (MTCC2656) by disc diffusion method. For the antibacterial assay, standard inoculums (1–2 × 10⁷ c.f.u/mL 0.5 McFarland standards) were introduced onto the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculums. The discs measuring 6.26 mm in diameter were prepared from Whatman no. 1 filter paper and sterilized by dry heat at 140 °C for 1 h. The sterile discs previously soaked in a known concentration of the test compounds were placed in the nutrient agar medium. The plates were inverted and incubated for 24 h at 37 °C. The inhibition zones were measured and compared with the standard drug streptomycin. The zone of inhibition data are presented in Table 1. The antibacterial screening revealed that all the tested compounds 5a–e showed moderate to good inhibition towards all the tested strains. Compounds 5b, 5d, 5e, 6b, 6c and 6e exhibited potent inhibitory activity compared to the standard drug at the tested concentrations.

4. Antifungal Evaluation

Compounds 5a–e and 6a–e were also evaluated for in vitro antifungal activity against four fungi viz. Candida albicans (ATCC 10231), Aspergillus fumigates (HIC 6094), Trichophyton rubrum (IFO 9185) and Trichophyton mentagrophytes (IFO 40996) by agar diffusion method. For the antifungal assay 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 used to make a suspension of spore of fungal strain for lawnning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species. 20 mL of agar media was poured into each petri-dish, excess of suspension was decanted and the plates were dried by placing in an incubator at 37 °C for 1 h. Using agar punch, wells were made and each well was labeled. A control was also prepared in triplicate and maintained at 37 °C for 3–4 days. The C. albicans was grown for 48 h at 28 °C in YPD broth (1% yeast extract, 2% peptone and 2% dextrose), harvested by centrifugation and then washed twice with sterile distilled water. A. fumigatus, T. rubrum and T. mentagrophytes were plated in potato dextrose agar (PDA) (Difco) and incubated at 28 °C for two weeks. Spo-
res were washed three times with sterile distilled water and re-suspended in distilled water to obtain an initial inoculums size of 10^5 spores/mL. The zones of inhibition were determined and compared with the standard drug amphotericin B (Table 2). Results of antifungal activity showed that most of the new compounds, i.e. 5b, 5d, 5c, 6b, 6c and 6e were active with moderate to good activity.

5. Experimental

Commercial grade reagents were used as supplied. Solvents except analytical reagent grade were dried and purified according to literature when necessary. Reaction progress and purity of the compounds were checked by thin-layer chromatography (TLC) on pre-coated silica gel F254 plates from Merck and were visualized either by exposure to UV light or dipping in 1% aqueous KMnO4 solution. Silica gel chromatographic columns (60–120 mesh) were used for separations. All melting points are uncorrected and measured using Fisher–Johns apparatus. FT IR spectrometer. The 1H NMR and 13C NMR spectra were recorded as KBr disks on a Perkin–Elmer spectrometer. The 1H NMR and 13C NMR spectra were recorded on a Varian gemini spectrometer (300 MHz for 1H and 75 MHz for 13C). Chemical shifts are reported for 1H and 75 MHz for 13C).

Preparation of 5-(3-formyl-4-methoxybenzyl)-2-methoxybenzoic acid (3): To a solution of 2 (0.01 mol) and K$_2$CO$_3$ (0.04 mol) in DMF (16 mL), MeI (0.03 mol) was added. The reaction mixture was stirred for 12 h at room temperature (TLC, EtOAc : petroleum ether, 2:1). The reaction mixture was refluxed for 12 h at room temperature (TLC, EtOAc : petroleum ether, 2:1). The reaction mixture was concentrated and cooled to room temperature, and the remaining solvent was removed under reduced pressure, then diethyl ether (25 mL) was added and the reaction mixture was left at 0 °C for overnight. The precipitated solid was filtered off; the crude product thus obtained was purified by column chromatography on silica gel with hexane-ethyl acetate as eluent to afford the pure compounds 5a–e.

Bis[4-methoxy-3-(6-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)phenyl]methane (5a): Yield 82%; mp 230–232 °C; IR (KBr): $\nu_{\max}$ 2926, 1614, 1592, 1441, 1068, 796 cm$^{-1}$; 1H NMR (DMSO-$d_6$, 300 MHz): $\delta$ 9.42 (s, 2H, Ar-H), 6.95–7.60 (m, 12H, Ar-H), 6.51 (d, $J=9.1$ Hz, 2H, Ar-H), 4.22 (s, 2H, CH$_2$), 3.89 (s, 6H, OCH$_3$), 3.79 (s, 6H, OCH$_3$), 3.59 (s, 4H, CH$_2$-S); 13C NMR (DMSO-$d_6$, 75 MHz): $\delta$ 162.3, 156.6, 154.3, 135.1, 132.7, 131.3, 130.7, 129.7, 128.4, 127.9, 123.7, 117.6, 56.1, 42.0, 31.6; Anal. Calcd for C$_{35}$H$_{28}$N$_8$S$_2$: C, 64.01; H, 4.30; N, 17.0. Found: C, 63.96; H, 4.45; N, 17.05. MS: m/z 656 (M$^+$).

Bis[4-methoxy-3-(6-aryl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)phenyl]methane (5b): Yield 79%; mp 211–213 °C; IR (KBr): $\nu_{\max}$ 3235, 3072, 2926, 2850, 1614, 1592, 1441, 1068, 796 cm$^{-1}$; 1H NMR (DMSO-$d_6$, 300 MHz): $\delta$ 9.42 (s, 2H, Ar-H), 7.37 (d, $J=9.1$ Hz, 2H, Ar-H), 7.16 (d, $J=8.6$ Hz, 4H, Ar-H), 6.92 (d, $J=8.6$ Hz, 4H, Ar-H), 6.51 (d, $J=9.1$ Hz, 2H, Ar-H), 4.02 (s, 2H, CH$_2$), 3.89 (s, 6H, OCH$_3$), 3.79 (s, 6H, OCH$_3$), 3.59 (s, 4H, CH$_2$-S); 13C NMR (DMSO-$d_6$, 75 MHz): $\delta$ 162.3, 156.6, 154.3, 135.1, 132.7, 131.3, 130.7, 129.7, 128.4, 127.9, 123.7, 117.6, 56.1, 42.0, 31.6; Anal. Calcd for C$_{34}$H$_{32}$N$_8$S$_2$: C, 62.00; H, 4.45; N, 17.0. Found: C, 62.04; H, 4.44; N, 17.0. MS: m/z 656 (M$^+$).

Bis[4-methoxy-3-(6-aryl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)phenyl]methane (5c): Yield 69%; mp 241–243 °C; IR (KBr): $\nu_{\max}$ 3310, 3035, 2926, 2850, 1592, 1535, 1070, 746 cm$^{-1}$; 1H NMR (DMSO-$d_6$, 300 MHz): $\delta$ 9.42 (s, 2H, Ar-H), 7.37 (d, $J=9.1$ Hz, 2H, Ar-H), 7.20 (d, $J=8.6$ Hz, 4H, Ar-H), 6.67 (d, $J=8.6$ Hz, 4H, Ar-H), 6.51 (d, $J=9.1$ Hz, 2H, Ar-H), 4.02 (s, 2H, CH$_2$), 3.90 (s, 6H, OCH$_3$), 3.59 (s, 4H, CH$_2$-S); 13C NMR (DMSO-$d_6$, 75 MHz): $\delta$ 162.3, 156.6, 154.3, 135.1, 132.6, 131.3, 127.1, 123.7, 117.6, 113.2, 56.1, 48.7, 42.0; Anal. Calcd for C$_{34}$H$_{32}$N$_8$S$_2$: C, 62.0; H, 4.45; N, 15.63. Found: C, 62.04; H, 4.44; N, 15.58. MS: m/z 716 (M$^+$).

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Bis[4-methoxy-3-(6-(4-nitrophenyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiazadiazin-3-yl)phenyl]methane (5d): Yield 84%; mp 271–273 °C; IR (KBr): ν max 3035, 1618, 1595, 1532, 1370, 1069, 750 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ 9.42 (s, 2H, Ar-H), 8.40 (d, J = 8.4 Hz, 4H, Ar-H), 7.82 (d, J = 8.4 Hz, 4H, Ar-H), 7.37 (d, J = 9.1 Hz, 2H, Ar-H), 6.51 (d, J = 9.1 Hz, 2H, Ar-H), 4.02 (s, 2H, CH₂), 3.90 (s, 6H, OCH₃), 3.61 (s, 4H, CH₂-S); ¹³C NMR (DMSO-d₆, 75 MHz): δ 162.4, 1590, 1457, 1069, 750, 680 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ 9.50 (s, 2H, 2H, Ar-H), 7.90 (d, J = 8.3 Hz, 4H, Ar-H), 7.40–7.35 (m, 12H, Ar-H), 7.00 (d, J = 8.3 Hz, 4H, Ar-H), 6.90 (d, J = 9.1 Hz, 2H, Ar-H), 5.80 (dd, J XA = 11.4, J XB = 5.1 Hz, 2H, H X), 3.95 (s, 2H, CH₂), 3.91 (s, 6H, OCH₃), 2.31 (dd, J AB = 12.7, J BA = 5.1 Hz, 2H, H B); ¹³C NMR (DMSO-d₆, 75 MHz): δ 170.0, 160.0, 157.0, 154.2, 143.7, 136.6, 158.7, 152.4, 152.9, 150.0, 144.0, 137.1, 133.7, 131.6, 130.3, 129.8, 129.7, 129.0, 128.3, 127.7, 122.3, 118.1, 56.1, 55.3, 43.3, 42.0; Anal. Calcld for C₃₅H₂₆N₁₀O₆S₂: C, 56.29; H, 4.90; N, 13.23; MS: m/z 794 (M⁺).

General procedure for the synthesis of bis[4-methoxy-3-(6,8-diaryli)-7,8-dihydro[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepin-3-yl)phenyl]methanes 6a–e: To a mixture of 4 (0.01 mol) and the corresponding 1,3-diaryl-2-propylamine derivative (0.02 mol) in ethanol (50 mL) a few drops of glacial acetic acid was added and the reaction mixture refluxed for 5 h. At the end of the reaction, the ethanolic solution was concentrated to half of its volume under reduced pressure. The solid that separated from the concentrate was filtered and purified by column chromatography on silica gel with petrolether-ethyl acetate as eluent to afford the pure compounds 6a–e.

Bis[4-methoxy-3-(6,8-diphenyl)-7,8-dihydro[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepin-3-yl)phenyl]methane (6a): Yield 72%; mp 210–212 °C; IR (KBr): ν max 3059, 1618, 1595, 1530, 1370, 1068, 750 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ 9.32 (s, 2H, Ar-H), 7.69–7.66 (m, 6H, Ar-H), 7.50–7.35 (m, 12H, Ar-H), 7.24–7.16 (m, 4H, Ar-H), 6.69 (d, J = 9.1 Hz, 2H, Ar-H), 4.98 (dd, J AX = 11.4, J XB = 5.1 Hz, 2H, H X), 4.00 (s, 2H, CH₂), 3.91 (s, 6H, OCH₃), 2.31 (dd, J AB = 12.7, J BA = 11.4 Hz, 2H, H B), 2.13 (dd, J BX = 5.1, J BX = 12.7 Hz, 2H, H B); ¹³C NMR (DMSO-d₆, 75 MHz): δ 170.0, 158.7, 152.9, 152.4, 144.0, 142.6, 133.7, 131.6, 130.5, 129.8, 129.0, 128.3, 127.7, 127.1, 126.4, 122.3, 118.1, 56.1, 55.3, 43.3, 42.0; Anal. Calcld for C₉₆H₄₆N₂₀O₁₂S₂: C, 70.31; H, 4.82; N, 13.39; Found: C, 70.20; H, 4.85; N, 13.32; MS: m/z 838 (M⁺).
Bis[4-methoxy-3-(6-phenyl-8-(3-hydroxy-4-methoxyphenyl))-7,8-dihydro[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepin-3-yl)phenyl]methane (6e): Yield 74%; mp 249–251 °C; IR (KBr): ν max 3438, 3031, 2925, 1621, 1590, 1513, 1275, 1024, 750 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ 9.40 (s, 2H, Ar-H), 7.50–7.35 (m, 12H, Ar-H), 7.18 (d, J = 8.3 Hz, 2H, Ar-H), 7.11 (s, 2H, Ar-H), 6.69–6.58 (m, 4H, Ar-H), 4.76 (dd, Jₓₓ = 11.4, Jₓᵧ = 5.1 Hz, 2H, Hₓ), 4.49 (s, 2H, OH), 4.00 (s, 2H, CH₂), 3.92 (s, 6H, OCH₃), 2.31 (dd, Jᵧₓ = 11.4, Jᵧₐ = 12.7 Hz, 2H, Hᵧ); ¹³C NMR (DMSO-d₆, 75 MHz): δ 169.8, 158.4, 152.7, 150.1, 147.6, 143.8, 142.1, 133.9, 131.6, 129.7, 129.2, 127.9, 127.2, 123.0, 122.3, 118.1, 117.0, 116.4, 112.1, 59.6, 56.1, 55.7, 43.3, 42.0; Anal. Calcd for C₅₁H₄₄N₈O₆S₂: C, 65.93; H, 4.77; N, 12.06. Found: C, 65.88; H, 4.81; N, 12.05; MS: m/z 930 (M⁺ – 1).

Table 1. Antibacterial activity of 5a–e and 6a–e

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<th>C. violaceum</th>
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Streptomycin 25 30 30 30

* Streptomycin (50 μg / disc) was used as positive reference and compounds 5a–e and 6a–e (50 μg / disc) were screened.

Scheme 1. Synthetic route to methylene bis[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles and bis[4-methoxy-3-(6,8-diaryl)-7,8-dihydro[1,2,4]triazolo [3,4-b][1,3,4]thiadiazepinyl]phenyl)methane

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<th>Compounds</th>
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<th>c</th>
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<td>4-HO-C₆H₄</td>
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<td>6. Ar’ =</td>
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<td>4-NO₂-C₆H₄</td>
<td>3,4-di-Cl-C₆H₄</td>
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Reagents and conditions: (i) CH₂O, H₂SO₄, reflux; (ii) MeI, K₂CO₃, DMF, rt; (iii) Thiocarbohydrazide, heat; (iv) PhCOCH₃, EtOH, reflux. (v) PhCOCH=CHAr’, reflux.

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Table 2. Antifungal activity of 5a–e and 6a–e

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<tr>
<th>Compound</th>
<th>Minimum inhibition concentration (MIC) (μg/mL)</th>
<th>C. albicans</th>
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<th>T. rubrum</th>
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Streptomycin 30 30 25 25

a Amphotericin (100 μg / disc) was used as positive reference and compounds 5a–e and 6a–e (100 μg / disc) were screened.

6. Conclusions

A new series of bis[4-methoxy-3-(6-aryl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol)phenyl]methanes and bis[(triazolo[3,4-b]thiadiazepin-3-yl)phenyl]methanes 5a–e and 6a–e has been synthesized and evaluated for their antimicrobial activity against various bacterial and fungal strains. The screened compounds 5b, 5d, 5e, 6b, 6c and 6e exhibited potent antimicrobial activity compared to standard drug at the tested concentrations. Most of the other compounds also showed appreciable activity against the tested bacteria and fungi, and emerged as potential molecules for further development.

7. Acknowledgements

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8. References


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Povzetek

Pripravili smo novo serijo bis[4-metoksi-3-(6-aril-1,3,4-tiadiazin-3-il)fenil]metanov (5a–e) in 4-metoksi-3-(6-aril-1,3,4-tiadiazin-3-il)fenil]metanov (6a–e) ter nove spojine karakterizirali z IR, 1H in 13C NMR, MS ter elementno analizo. Vsem novim spojinam smo določili tudi antibakterijsko aktivnost proti testiranim bakterijam in glivam ter so se izkazale za potencialne molekule za nadaljnji razvoj.

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