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Synthesis and biological activities evaluation of some new 1,2,4–triazinone derivatives bearing sulfonamide moiety

Abstract

This paper describes the synthesis of a new series of functionalized 1,2,4–triazinones and containing sulfonamide moieties by 1,3–dipolar cyclocondensation reaction of nitrilimines with α–amino–esters. The structures of the newly synthesized compounds were elucidated by spectral methods (IR, ^{1}H–NMR, ^{13}C–NMR and MS spectrometry) and elemental analysis. The newly synthesized compounds were screened for their *in vitro* antimicrobial activity. Some of titled compounds exhibited significant antimicrobial activity on several strains of microbes

Keywords: nitrilimines, α–aminoesters, sulfa drugs, antimicrobial activity, 1,2,4–triazinones, HZ, TMS

Volume 1 Issue 7 - 2017

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Received: November 17, 2017 | **Published:** December 28, 2017

Introduction

Sulfa drugs are sulfonamide antibiotics and they are synthetic antimicrobial agents with widely uses for the treatment of various infectious diseases.[1–7] These drugs were the first efficient treatment to be employed systematically for the prevention and cure of bacterial infections.[8–11] One of the first sulfonamides identified by Domagk et al.[8,9] was the red azo dye known as Prontosil.[8,9] It was active against streptococcal infection *in vivo*. There have been many analogues of sulfanilamide developed as pharmacological agents that display a wide range of biological activities.[12,13] For example, glibenclamide has found use as a hypoglycemic agent, indisulam (E7070) as an anticancer agent, amprenavir and tipranavir are used in HIV therapy, Furosemide as a diuretic, acetazolamide as a carbonic anhydrase inhibitor, and sulfathiazole, sulfaquinoxaline, silver sulfadiazine (silvadene®), sulfasalazine (azulfidine®) and sulfamethoxazole (gantanol®) as an antibacterial agents.[7,10,11,14–16] In addition, dorzolamide, and brinzolamide have been launched as topically acting antiglaucoma pharmacological agents.[17,18] Till date, thousands of sulfonamide derivatives, analogues, and related compounds have been synthesized, which are effective as diuretics, anti–malarial, leprosy and antithyroid agents and employed for other diseases.[17,19] Moreover, aryl sulfonamides celecoxib and vadecoxib are used as COX–II inhibitors and anticancer agents.[20,21] Sildenafil was launched in 1998 as an anti–impotence drug and responsible for inhibiting the degradation of cyclic guanosine monophosphate.[22] It has been observed that sulfa drugs show increased biological activity when administered in the form of metal complexes.[18,23]

The development of nitrogen and sulfur containing heterocyclic compounds in medicinal chemistry and pharmaceutical communities as these molecules has potent biological activities. Among them, 1,2,4–triazine derivatives are known to exhibit various pharmacological[24] and medicinal applications.[25–27] Taking into account all previous commentaries of the biological activities of sulfonamides and in continuation of our study on the synthesis of biologically active heterocycles,[28,29] efforts have been made to synthesize a series of new 1,2,4–triazinone derivatives incorporating sulfonamide moiety via cyclocondensation reaction of nitrilimines bearing moiety of sulfonamide with α–aminoesters in anticipation of expected interesting biological activities.

Materials and methods

Apparatus and chemicals

Melting points were determined using an electro thermal melting temperature apparatus and are uncorrected. The IR spectra were measured as KBr pellets using a Satellite 3000 Mid infrared spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 300MHz spectrometer at room temperature in DMSO–d_6 solution using tetramethyl silane (TMS) as internal reference. Chemical shifts are expressed in δ (ppm) downfield from TMS and coupling constants are in Hertz (Hz). Electron impact (EI) mass spectra were run on a Shimadzu GCMS–QP1000 EX spectrometer at 70eV. Elemental analysis was carried out at micro analytical laboratory, Cairo University, Cairo, Egypt. Ethyl mercapto acetate 6 was purchased from Avocado Research Chemicals, England, and used without further purification. Hydrazonoyl chlorides 1a–c employed in this study, were prepared via direct coupling of the appropriate sulfa drug diazonium chloride with α–chloroacetoacetanilide in sodium acetate/ethanol solution following standard procedures.[30] α–Aminoester hydrochlorides 3 employed in this work were obtained by reacting the appropriate α–amino acids with thionyl chloride in excess methanol following reported procedures.[31]

General procedure for synthesis of 1,2,4–triazinones 5a–o.

To a stirred solution of the appropriate hydrazonoyl halides (5mmol) in tetrahydrofuran (70mL) was added a solution of the particular α–aminoester hydrochloride (10mmol) in methanol (30mL). To the resulting reaction mixture, cooled in an ice–salt bath (–5–0°C),

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was drop wise added triethylamine (30mmol). After addition was complete, stirring was continued for 2–4 hours at 0°C, and then at room temperature overnight. The solvent was removed under reduced pressure, and the residue was washed with water. The resulting solid product was collected and recrystallized from ethanol/water solution to give the desired 4,5–dihydro–1,2,4–triazinones 5a–o. The following compounds were prepared using this method:

3–phenylaminocarbonyl–1–[4–(thizol–2–yl–sulfamoyl) phenyl]–4,5–dihydro–1,2,4–triazin–6–one (5a): Yield 71%, m.p. 248–250°C. IR (KBr): cm^{-1} 3360, 3272, 3246 (NH), 1675 (lactam C=O), 1655 (amide C=O), 1630 (C=N), 1346, 1145 (SO_2). ^{1}H NMR (DMSO–d_6): δ/ppm 12.63 (s, 1H, SO_2NH), 10.96 (s, 1H, PhNH), 8.71 (d, 1H, thiazole), 7.93–7.04 (m, 9H, aromatic), 6.62 (d, 1H, thiazole), 6.35 (s, 1H, NH triazinone ring), 4.32 (s, 2H, CH_2); ^{13}C NMR (DMSO–d_6): δ/ppm 160.33 (lactam C=O), 157.10 (amide C=O), 139.34 (C=N), 142.21–119.12 (8 Ar–C), 168.02, 135.45, 116.50 (3 thiazole–C), 43.77 (CH_2). MS: m/z=456 [M^+]. Anal. Calcd. for $C_{19}H_{16}N_6O_4S_2$ (456.51): C, 49.99; H, 3.53; N, 18.41; Found C, 50.24; H, 3.65; N, 18.32.

5–Methyl–3–phenylaminocarbonyl–1–[4–(thizol–2–yl–sulfamoyl) phenyl]–4,5–di–hydro–1,2,4–tri–azin–6–one (5b): Yield 68%, m.p. 235–237°C. IR (KBr): cm^{-1} 3355, 3273, 3242 (NH), 1676 (lactam C=O), 1650 (amide C=O), 1628 (C=N), 1349, 1142 (SO_2); ^{1}H NMR (DMSO–d_6): δ/ppm 12.66 (s, 1H, SO_2NH), 10.02 (s, 1H, PhNH), 8.68 (d, 1H, thiazole), 7.96–7.05 (m, 9H, aromatic), 6.60 (d, 1H, thiazole), 6.32 (s, 1H, NH triazinone ring), 4.42–4.36 (q, 1H, CH), 1.58–1.56 (d, 3H, CH_3); ^{13}C NMR (DMSO–d_6): δ/ppm 160.25 (lactam C=O), 157.3 (amide C=O), 139.31 (C=N), 141.94–119.18 (8 Ar–C), 168.00, 135.42, 116.46 (3 thiazole–C), 49.68 (CH), 19.87 (CH_3). MS: m/z=470 [M^+]. Anal. Calcd. for $C_{22}H_{22}N_6O_4S_2$ (470.53): C, 51.05; H, 3.86; N, 17.86; Found C, 50.90; H, 3.98; N, 17.75.

5–Isopropyl–3–phenylaminocarbonyl–1–[4–(thizol–2–yl–sulfamoyl)phenyl]–4,5–dihydro–1,2,4–tri–azin–6–one (5c): Yield 65%, m.p. 240–242°C. IR (KBr): cm^{-1} 3360, 3268, 3246 (NH), 1673 (lactam C=O), 1652 (amide C=O), 1634 (C=N), 1343, 1137 (SO_2); ^{1}H NMR (DMSO–d_6): δ/ppm 12.62 (s, 1H, SO_2NH), 10.98 (s, 1H, PhNH), 8.73 (d, 1H, thiazole), 7.98–7.06 (m, 9H, aromatic), 6.62 (d, 1H, thiazole), 6.32 (s, 1H, NH triazinone ring), 4.25–4.23 (d, 1H, CH), 2.58–2.40 (m, 1H, CH), 1.12–1.05 (d, 6H, $2CH_3$); ^{13}C NMR (DMSO–d_6): δ/ppm 160.72 (lactam C=O), 157.70 (amide C=O), 139.00 (C=N), 141.98–119.82 (8 Ar–C), 167.92, 135.32, 116.57 (3 thiazole–C), 59.36 (CH), 32.87 (CH), 18.32, 16.76 (2 CH_3). MS: m/z=498[M^+]. Anal. Calcd. for $C_{22}H_{22}N_6O_4S_2$ (498.59): C, 53.00; H, 4.45; N, 16.86; Found C, 53.25; H, 4.35; N, 16.97.

5–Benzyl–3–phenylaminocarbonyl–1–[4–(thizol–2–yl–sulfamoyl) phenyl]–4,5–di–hydro–1,2,4–tri–azin–6–one (5d): Yield 70%, m.p. 234–236°C. IR (KBr): cm^{-1} 3376, 3273, 3239 (NH), 1678 (lactam C=O), 1656 (amide C=O), 1634 (C=N), 1344, 1135 (SO_2); ^{1}H NMR (DMSO–d_6): δ/ppm 12.65 (s, 1H, SO_2NH), 11.01 (s, 1H, PhNH), 8.74 (d, 1H, thiazole), 7.96–7.02 (m, 14H, aromatic), 6.66 (d, 1H, thiazole), 6.35 (s, 1H, NH triazinone ring), 4.55–4.52 (t, 1H, CH), 3.26–3.18 (d, 1H, CH_2); ^{13}C NMR (DMSO–d_6): δ/ppm 161.37 (lactam C=O), 157.37 (amide C=O), 139.70 (C=N), 142.19–119.29, (12 Ar–C), 168.02, 135.42, 116.17 (3 thiazole–C), 55.64 (CH), 40.43 (CH_2). MS: m/z=546 [M^+]. Anal. Calcd. for $C_{26}H_{22}N_6O_4S_2$ (546.63): C, 57.13; H, 4.06; N, 15.37; Found C, 56.90; H, 3.95; N, 15.52.

5–Phenyl–3–phenylaminocarbonyl–1–[4–(thizol–2–yl–sulfamoyl) phenyl]–4,5–di–hydro–1,2,4–tri–azin–6–one (5e): Yield 62%, m.p. 254–256°C. IR (KBr): cm^{-1} 3375, 3273, 3236 (NH), 1675 (C=O lactam), 1650 (amide C=O), 1631 (C=N), 1349, 1148 (SO_2); ^{1}H NMR (DMSO–d_6): δ/ppm 12.67 (s, 1H, SO_2NH), 11.03 (s, 1H, PhNH), 8.76 (d, 1H, thiazole), 7.95–7.03 (m, 14H, aromatic), 6.64 (d, 1H, thiazole), 6.33 (s, 1H, NH triazinone ring), 5.35 (s, 1H, CH); ^{13}C NMR (DMSO–d_6): δ/ppm 160.78 (lactam C=O), 157.76 (amide C=O), 139.10 (C=N), 142.11–119.83 (12 Ar–C), 167.96, 135.35, 116.12 (3 thiazole–C), 56.80 (CH). MS: m/z=532 [M^+]. Anal. Calcd. for $C_{25}H_{20}N_6O_4S_2$ (532.60): C, 56.38; H, 3.79; N, 15.78; Found C, 56.60; H, 3.90; N, 15.65.

3–phenylaminocarbonyl–1–[4–(pyrimidin–2–yl–sulfamoyl) phenyl]–4,5–dihydro–1,2,4–triazin–6–one (5f): Yield 72%, m.p. 275–277°C. IR (KBr): cm^{-1} 3387, 3261, 3229 (NH), 1681 (lactam C=O), 1655 (amide C=O), 1627 (C=N), 1350, 1155 (SO_2); ^{1}H NMR (DMSO–d_6): δ/ppm 12.62 (s, 1H, SO_2NH), 10.97 (s, 1H, PhNH), 7.93–7.02 (m, 9H, aromatic), 8.41 (d, 2H, pyrimidine), 6.83 (t, 1H, pyrimidine), 6.40 (s, 1H, NH triazinone ring), 4.34 (s, 2H, CH2); ^{13}C NMR (DMSO–d_6): δ/ppm 161.50 (lactam C=O), 158.74 (amide C=O), 141.04 (C=N), 142.61–116.20 (8 Ar–C), 168.42, 156.62, 110.54 (3 pyrimidine–C), 43.92 (CH_2). MS: m/z = 451 [M^+]. Anal. Calcd. for $C_{20}H_{17}N_7O_4S$ (451.47): C, 53.21; H, 3.80; N, 21.72; Found C, 53.01; H, 3.91; N, 21.62.

5–Methyl–3–phenylaminocarbonyl–1–[4–(pyrimidin–2–yl–sulfamoyl)phenyl]–4,5–dihydro–1,2,4–tri–azin–6–one (5g): Yield 70%, m.p. 258–260°C. IR (KBr): cm^{-1} 3358, 3264, 3220 (NH), 1682 (lactam C=O), 1657 (amide C=O), 1626 (C=N), 1356, 1149 (SO_2); ^{1}H NMR (DMSO–d_6): δ/ppm 12.65 (s, 1H, SO_2NH), 10.94 (s, 1H, PhNH), 7.91–6.93 (m, 9H, aromatic), 8.32 (d, 2H, pyrimidine), 6.86 (t, 1H, pyrimidine), 6.41 (s, 1H, NH triazinone ring), 4.41–4.35 (q, 1H, CH), 1.58–1.56 (d, 3H, CH_3); ^{13}C NMR (DMSO–d_6): δ/ppm 161.55 (lactam C=O), 158.77 (amide C=O), 141.60 (C=N), 142.15–115.87 (8 Ar–C), 168.42, 156.67, 110.43 (3 pyrimidine–C), 49.88 (CH), 19.85 (CH_3). MS: m/z=465 [M^+]. Anal. Calcd. for $C_{21}H_{19}N_7O_4S$ (465.49): C, 54.19; H, 4.11; N, 21.06; Found C, 53.95; H, 3.98; N, 20.94.

5–Isopropyl–3–phenylaminocarbonyl–1–[4–(pyrimidin–2–yl–sulfamoyl)phenyl]–4,5–dihydro–1,2,4–triazin–6–one (5h): Yield 74%, m.p. 266–268°C. IR (KBr): cm^{-1} 3375, 3258, 3232 (NH), 1677 (lactam C=O), 1655 (amide C=O), 1628 (C=N), 1353, 1155 (SO_2); ^{1}H NMR (DMSO–d_6): δ/ppm 12.63 (s, 1H, SO_2NH), 10.97 (s, 1H, PhNH), 7.90–6.96 (m, 9H, aromatic), 8.48 (d, 2H, pyrimidine), 6.85 (t, 1H, pyrimidine), 6.38 (s, 1H, NH triazinone ring), 4.31 (d, 1H, CH), 2.58–2.41 (m, 1H, CH), 1.14–1.08 (d, 6H, $2CH_3$); ^{13}C NMR (DMSO–d6): δ/ppm 161.73 (lactam C=O), 158.73 (amide C=O), 141.00 (C=N), 142.73–116.25 (8 Ar–C), 168.18, 156.52, 110.41 (3 pyrimidine–C), 59.65 (CH), 33.19 (CH), 18.60, 16.82 (2 CH_3). MS: m/z=493 [M^+]. Anal. Calcd. for $C_{23}H_{23}N_7O_4S$ (493.55): C, 55.97; H, 4.70; N, 19.87; Found C, 56.20; H, 3.82; N, 19.66.

5–Benzyl–3–phenylaminocarbonyl–1–[4–(pyrimidin–2–yl–sulfamoyl)phenyl]–4,5–dihydro–1,2,4–tri–azin–6–one (5i): Yield 67%, m.p. 229–231 °C. IR (KBr): cm^{-1} 3366, 3261, 3231 (NH), 1685 (lactam C=O), 1652 (amide C=O), 1626 (C=N), 1351, 1156 (SO_2); ^{1}H NMR (DMSO–d_6): δ/ppm 12.62 (s, 1H, SO_2NH), 10.96 (s, 1H, PhNH), 7.98–7.00 (m, 14H, aromatic), 8.61 (d, 2H, pyrimidine), 6.83 (t, 1H, pyrimidine), 6.35 (s, 1H, NH triazinone ring), 4.52–4.48 (t, 1H, CH), 3.22–3.14 (d, 2H, CH_2); ^{13}C NMR (DMSO–d6): δ/ppm 161.37 (lactam C=O), 158.67 (amide C=O), 141.70 (C=N), 142.40–116.39, (12 Ar–C), 168.09, 156.12, 110.19 (3 pyrimidine–C), 55.71(CH), 40.59 (CH_2). MS: m/z=541 [M^+]. Anal. Calcd. for $C_{27}H_{23}N_7O_4S$ (541.59): C, 59.88; H, 4.28; N, 18.10; Found C, 60.10; H, 4.37; N, 17.98.

5–Phenyl–3–phenylaminocarbonyl–1–[4–(pyrimidin–2–yl–sulfamoyl)phenyl]–4,5–dihydro–1,2,4–triazin–6–one (5j): Yield 70%, m.p. 263–265°C. IR (KBr): cm^{-1} 3356, 3255, 3234 (NH), 1683 (C=O lactam), 1656 (amide C=O), 1627 (C=N), 1356, 1152 (SO_2); ^{1}H NMR (DMSO–d6): δ/ppm 12.63 (s, 1H, SO_2NH), 11.02 (s, 1H, PhNH), 7.95–6.94 (m, 14H, aromatic), 8.64 (d, 2H, pyrimidine), 6.86 (t, 1H, pyrimidine), 6.36 (s, 1H, NH triazinone ring), 5.34 (s, 1H, CH); ^{13}C NMR (DMSO–d_6): δ/ppm 161.75 (lactam C=O), 158.67 (amide C=O), 141.10 (C=N), 142.38–116.14 (12 Ar–C), 168.22, 156.10, 110.14 (3 pyrimidine–C), 56.86 (CH). MS: m/z=527 [M^+]. Anal. Calcd. for $C_{23}H_{21}N_7O_4S$ (527.57): C, 59.19; H, 4.01; N, 18.58; Found C, 58.95; H, 3.92; N, 18.69.

3–phenylaminocarbonyl–1–[4–(5–methyloxazol–3–yl–sulfamoyl) phenyl]–4,5–di–hydro–1,2,4–tri–azin–6–one (5k): Yield 63%, m.p. 268–270°C. IR (KBr): cm^{-1} 3360, 3272, 3224 (NH), 1676 (lactam C=O), 1655 (amide C=O), 1622 (C=N), 1341, 1175 (SO_2). ^{1}H NMR (DMSO–d_6): δ/ppm 12.59 (s, 1H, SO_2NH), 10.92 (s, 1H, PhNH), 7.92–7.04 (m, 9H, aromatic), 6.38 (s, 1H, NH triazinone ring), 6.21 (s, 1H, oxazole proton), 4.30 (s, 2H, CH_2), 2.35 (s, 3H, CH_3 of oxazole nucleus); ^{13}C NMR (DMSO–d_6): δ/ppm 160.33 (lactam C=O), 157.84 (amide C=O), 140.68 (C=N), 140.96–119.21 (8 Ar–C), 168.30, 155.61, 95.23 (oxazole–C), 43.77 (CH2), 12.36 (CH_3). MS: m/z = 454 [M^+]. Anal. Calcd. for $C_{20}H_{18}N_6O_5S$ (454.47): C, 52.86; H, 3.99; N, 18.49; Found C, 52.65; H, 4.10; N, 18.38.

5–Methyl–3–phenylaminocarbonyl–1–[4–(5–methyloxazol–3–yl–sulfamoyl)–phenyl]–4,5–dihydro–1,2,4–triazin–6–one (5l): Yield 66%, m.p. 235–237°C. IR (KBr): cm^{-1} 3355, 3273, 3228 (NH), 1675 (lactam C=O), 1654 (amide C=O), 1626 (C=N), 1348, 1177 (SO_2); ^{1}H NMR (DMSO–d_6): δ/ppm 12.57 (s, 1H, SO_2NH), 10.93 (s, 1H, PhNH), 7.94–7.05 (m, 9H, aromatic), 6.35 (s, 1H, NH triazinone ring), 6.28 (s, 1H, oxazole proton), 4.40–4.34 (q, 1H, CH), 2.34 (s, 3H, CH_3 on oxazole ring), 1.62–1.58 (d, 3H, CH_3); ^{13}C NMR (DMSO–d6): δ/ppm 160.55 (lactam C=O), 157.78 (amide C=O), 140.31 (C=N), 140.94–119.28 (8 Ar–C), 168.24, 155.80, 95.23 (oxazole–C), 49.42 (CH), 19.77 (CH_3), 12.74 (CH_3 oxazole). MS: m/z=468 [M^+]. Anal. Calcd. for $C_{21}H_{20}N_6O_5S$ (468.49): C, 53.84; H, 4.30; N, 17.94; Found C, 54.07; H, 3.18; N, 18.05.

5–Isopropyl–3–phenylaminocarbonyl–1–[4–(5–methyloxazol–3–yl–sulfamoyl)phenyl]–4,5–di–hydro–1,2,4–triazin–6–one (5m): Yield 65%, m.p. 260–262°C. IR (KBr): cm^{-1} 3360, 3267, 3223 (NH), 1678 (lactam C=O), 1658 (amide C=O), 1623 (C=N), 1346, 1175 (SO_2); ^{1}H NMR (DMSO–d_6): δ/ppm 12.55 (s, 1H, SO_2NH), 10.96 (s, 1H, PhNH), 7.92–7.03 (m, 9H, aromatic), 6.37 (s, 1H, NH triazinone ring), 6.24 (s, 1H, oxazole proton), 4.35–4.24 (d, 1H, CH), 2.58–2.46 (m, 1H, CH), 2.33 (s, 3H, CH_3 on oxazole ring), 1.12–1.06 (d, 6H, $2CH_3$); ^{13}C NMR (DMSO–d6): δ/ppm 160.82 (lactam C=O), 157.79 (amide C=O), 139.96 (C=N), 141.01–119.82 (8 Ar–C), 168.30, 155.63, 96.02 (oxazole–C), 59.23 (CH), 32.85 (CH), 18.32, 16.71 (2 CH_3), 12.34 (CH_3 oxazole). MS: m/z=512 [M^+]. Anal. Calcd. for $C_{24}H_{28}N_6O_5S$ (512.59): C, 56.24; H, 5.51; N 16.40; Found C, 55.98; H, 5.60; N, 16.51.

5–Benzyl–3–phenylaminocarbonyl–1–[4–(5–methyloxazol–3–yl–sulfamoyl)–phenyl]–4,5–dihydro–1,2,4–triazin–6–one (5n): Yield 60%, m.p. 246–248°C. IR (KBr): cm^{-1} 3376, 3273, 3224 (NH), 1680 (lactam C=O), 1655 (amide C=O), 1622 (C=N), 1345, 1170 (SO_2); ^{1}H NMR (DMSO–d_6): δ/ppm 12.53 (s, 1H, SO_2NH), 10.94 (s, 1H, PhNH), 7.96–7.04 (m, 14H, aromatic), 6.35 (s, 1H, NH triazinone ring), 6.26 (s, 1H, oxazole proton), 4.55–4.52 (t, 1H, CH), 3.24–3.15 (d, 2H, CH_2), 2.38 (s, 3H, CH3); ^{13}C NMR (DMSO–d_6): δ/ppm 161.37 (lactam C=O), 158.17 (amide C=O), 140.21 (C=N), 140.69–119.19, (12 Ar–C), 167.97, 155.63, 96.02 (oxazole–C), 55.16 (CH), 40.46 (CH_2), 12.33 (CH_3). MS: m/z=544 [M^+]. Anal. Calcd. for $C_{27}H_{24}N_6O_5S$ (544.59): C, 59.55; H, 4.44; N, 15.43; Found C, 59.34; H, 4.35; N, 15.52.

5–Phenyl–3–phenylaminocarbonyl–1–[4–(5–methyloxazol–3–yl–sulfamoyl)–phenyl]–4,5–dihydro–1,2,4–triazin–6–one (5o): Yield 67%, m.p. 256–258°C. IR (KBr): cm^{-1} 3355, 3271, 3220 (NH), 1675 (C=O lactam), 1650 (amide C=O), 1615 (C=N) 1342, 1172 (SO_2); ^{1}H NMR (DMSO–d_6): δ/ppm 12.51 (s, 1H, SO_2NH), 10.98 (s, 1H, PhNH), 7.94–7.03 (m, 14H, aromatic), 6.39 (s, 1H, NH triazinone ring), 6.21 (s, 1H, oxazole proton), 5.33 (s, 1H, CH), 2.38 (s, 3H, CH_3); ^{13}C NMR (DMSO–d6): δ/ppm 160.87 (lactam C=O), 157.76 (amide C=O), 139.94 (C=N), 140.03–119.03 (12 Ar–C), 167.78, 155.81, 95.32 (oxazole–C), 56.38 (CH), 12.32 (CH_3). MS: m/z=530 [M^+]. Anal. Calcd. for $C_{26}H_{22}N_6O_5S$ (530.57): C, 58.86; H, 4.18, N; 15.84; Found C, 59.05; H, 4.05; N, 15.72.

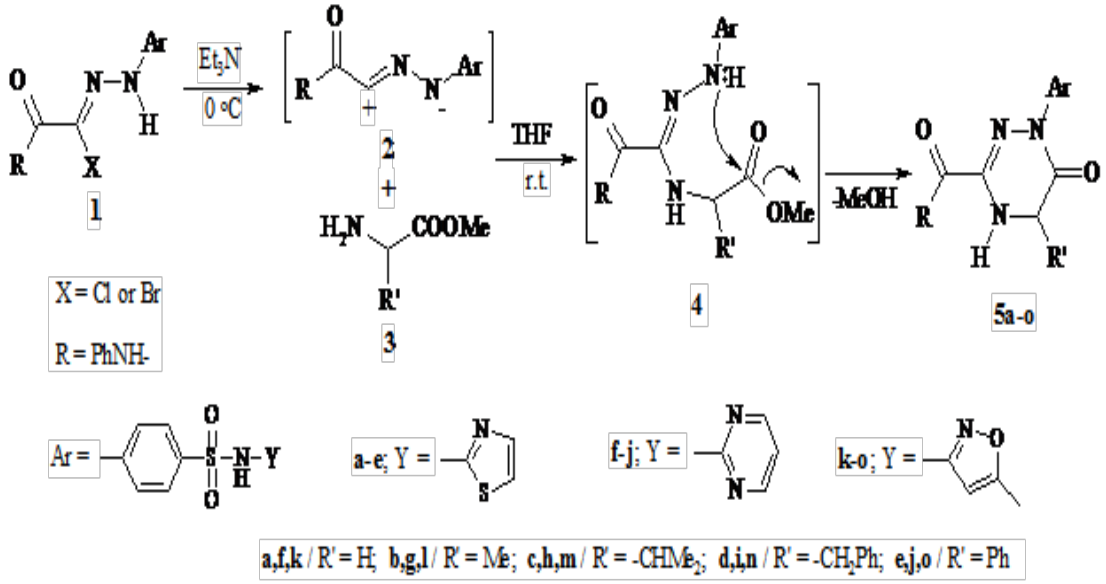
Results and discussion

The required nitrilimines 2 having sulfonamide moieties were generated in situ from the respective hydrazonoyl chlorides 1 upon the action of base, and found to react with α–aminoester hydrochlorides 3 at low temperature in the presence of triethylamine to give sulfomylphenyl–4,5–dihydro–1,2,4–triazin–6–ones 5a–o (Figure 1). The formation of these triazinones can be considered to involve an initial nucleophilic addition of an α–amino acid methyl esters 3 to the nitrilimines 2 yielding the open–chain amidrazone ester intermediate 4, which cyclized to produce 4,5–dihydro–1,2,4–triazinones 5a–o with the elimination of methanol. According to Baldwin, this type of cyclization is classified as an allowed 6–exo–trig process.[32] No investigations were carried out concerning optical purity and activity. The characteristic data of compounds 5a–o are given in details in the experimental section.

Spectral data analysis for compounds 5a–o

All compounds gave satisfactory combustion analysis for the proposed structures which were confirmed on the basis of their spectroscopic data. The mass spectra of the synthesized 1,2,4–triazin–6–ones 5a–o displayed the correct molecular ion peaks (M^+) in accordance with the suggested structures and showed the loss of methanol molecule (Experimental part). A main fragmentation mode of the closely related substituted 4,5–dihydro–1,2,4–triazin–6–ones was reported to involve hetero ring–scission, leading to fragment ion M–29 as a base peak for compounds 5a,f,k, for compounds 5b,g,l is M–43, for compounds 5c,h,m is M–71, for compounds 5d,i,n is M–119 and the base peak for compounds 5e,j,o is M–105.[33]

The IR spectra of compounds 5a–o in KBr revealed the presence of three NH absorption bands in the region 3370–3220cm^{-1}. The lactam carbonyl (C=O) appeared in the region 1680–1670cm^{-1}, and the amide C=O at about 1655cm^{-1}. The stretching band of C=N of triazinone ring appeared in the region 1630–1610cm^{-1}. The sharp bands appeared around 1340 and 1140cm^{-1} attributed to SO_2 of sulfonamide group. The ^{1}H NMR spectra of compounds 5a–o showed all the signals of the proposed structures, indicating the appearance of three NH proton signals as singlets at 12.6–12.5ppm (SO_2NH), 11.0–10.9ppm (PhNH) and 6.4–6.3ppm (NH of triazinone ring).



Scheme 1 Synthetic pathway of sulfamoylphenyl-4,5-dihydro-1,2,4-triazin-6-ones 5a-o.

Furthermore, the signals of thiazole ring protons appeared as a doublet at 8.7, 6.6ppm for compounds 5a–e, signals of pyrimidine ring protons as doublet at 8.6 and triplet at 6.8ppm for compounds 5f–j, and signal of oxazole ring proton appeared as a singlet at 6.3–6.2ppm for compounds 5k–o. Other signals can be concluded as follows: for compounds 5a,f,k containing a glycine residue, methylene protons appeared as a singlet in the range of 4.3–4.0ppm, in addition to the signals of aromatic protons. For compounds 5b, g, l containing an alanine rest, methyl protons appeared as doublets in the range of 1.6–1.5ppm and methinyl proton appeared as a quartet in the range of 4.4–4.3ppm, in addition to the signals resulting from the protons of the aromatic rings. In compounds 5c, h, m containing a valine residue, methyl proton signals appeared as a doublet in the range 1.2–1.0ppm, a methinyl proton as a multiplet in the range of 2.6–2.4ppm, and the ring methinyl proton as a doublet in the range of 4.3–4.2ppm, in addition to the signals of aromatic protons. For compounds 5d, i, n containing phenyl alanine rest, methylene protons of the benzyl group appeared as a doublet in the range 3.2–3.1ppm. The methinyl proton appeared as a triplet in the range of 4.5–4.4ppm, in addition to the signals resulting from the protons of the aromatic rings. In compounds 5e, j, o containing a phenyl glycine residue, the methinyl proton appeared as a singlet in the range of 5.4–5.3ppm, in addition to the signals of aromatic protons. The entire ^{1}H NMR data are presented in the Experimental Section.

The structure of the prepared compounds 5a–o is also supported by ^{13}C NMR measurements which displayed the characteristic signals of the suggested structures. The signal of the carbonyl carbon of the amide group appeared in the range of 158–157ppm, and that of the lactam resonated in the range of 161–160ppm. The signal at about 141–139ppm, is attributed to C=N of the triazinone ring, in addition to those recorded for the different carbons of thiazole, pyrimidine and oxazole rings. The ^{13}C NMR spectral data of the synthesized compounds are presented in the Experimental part.

Antimicrobial activity

Various sulfonamide moieties substituents were placed on the triazinone and thiadiazinone rings in order to study their effects on an antimicrobial activity in vitro. Most of the synthesized compounds were screened in vitro for their antimicrobial activity against a variety of bacterial strains such as Enterococci, Escherichia coli, Staphylococcus aureus, Klebsiella spp, Proteus spp, and fungi such as Aspergillus niger, Candida albicans, employing the nutrient agar disc diffusion method[34,35] at 1–100mg/mL concentration in dimethyl sulfoxide (DMSO) which used as solvent control, by measuring the average diameter of the inhibition zone in mm. All experiments were carried out in triplicate. The results showed that all the tested compounds exhibited good degree of activity against different strains of bacteria and fungi compared with well–known antibacterial and antifungal substances such as tetracycline and fluconazole respectively. The results are given in Table 1.

Table 1 Antimicrobial screening results of the tested compounds*

Comp.	Antibacterial Activity					Antifungal Activity	
No.	En.	E. coli	S. aureus	K. spp	P. spp	C. alb.	A. niger
5a	16	18	16	16	15	19	18
5b	18	19	14	15	17	20	19
5c	17	14	15	17	14	18	18
5d	16	19	17	18	15	20	19
5e	17	17	17	19	13	19	19
5f	15	14	15	18	16	17	18

Table Continued..

Comp.	Antibacterial Activity					Antifungal Activity	
No.	En.	E. coli	S. aureus	K. spp	P. spp	C. alb.	A. niger
5g	19	16	14	15	19	16	15
5h	18	15	18	17	17	17	16
5i	16	16	17	14	14	18	16
5j	14	14	16	15	16	16	17
5k	16	17	14	13	15	17	15
5l	14	16	12	14	17	18	16
5m	19	17	18	19	18	19	18
5n	17	15	15	16	15	16	16
5o	18	19	16	17	14	14	18
DMSO	--	--	--	--	--	--	--

*All experiments were carried out in triplicate and measuring the average diameter of the inhibition zone in mm.

Ent.: Enterococci, E. coli = Escherichia coli, S. aureus = Staphylococcus aureus, K. spp = Klebsiella spp, P. spp = Proteus spp, C. alb. = Candida albicans, A. niger =Aspergillus niger.

According to NCCLS,[36] zones of inhibition for tetracycline and fluconazole <14mm were considered resistant, between 15 and 18mm were considered weakly sensitive and >19mm were considered sensitive. From the screening results, it found to possess various antimicrobial activities towards all the microorganisms tested. The results confirm that, the antimicrobial activity is strongly dependent on the nature of the substituents on triazinone and thiadiazinone nucleus. The presence of sulfonamide moieties showed a better spectrum of activity than the reference drug (Table 1).

Conclusion

New series of novel functionalized 1,2,4–triazinones 5a–o containing benzene sulfonamide moiety were synthesized using hydrazonoyl halides as a precursor of nitrilimines and evaluated for their in vitro antibacterial, and antifungal activities. From the screening results, it found to possess various antimicrobial activities towards all the microorganisms tested. The results confirm that, the antimicrobial activity is strongly dependent on the nature of the substituents on triazinone nucleus. The pyrimidinyl, thiazolyl methoxzolyl derivatives generally led to dramatic improvements in activity against both bacteria and fungi. In short, the present study can lead medicinal chemists to design and synthesize similar compounds with enhanced biological potency in future.

Acknowledgements

The authors are great thankful to the Qatar Charity for the financial support of this research through Ibhath grant (GCC–07–06).

Conflict of interest

The author declares no conflict of interest.

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