European Journal of Chemistry 5 (3) (2014) 481-487

European Journal of Chemistry

Journal homepage: www.eurjchem.com

Synthesis and antimicrobial evaluation of some 1,2,4-triazolo[1,5-a]pyridine, pyrimidine sulfonamides and sulfinyl derivatives

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ARTICLE INFORMATION

DOI: 10.5155/eurjchem.5.3.481-487.1054

Received: 18 March 2014
Received in revised form: 20 April 2014
Accepted: 24 April 2014
Online: 30 September 2014

KEYWORDS

Sulfinyl
Pyrimidine
Benzooxazole
Sulfonamides
Benzimidazole
Triazolopyridine

ABSTRACT

Several new substituted sulfonamides and sulfinyl compound derivatives were obtained by the reaction of 2-thioxo-1,2,4-triazolo[1,5-a]pyridine and pyrimidine thiol derivatives with (2-chloromethyl)benzimidazole and/or (2-chloromethyl)benzooxazole. Structures of the newly synthesized products have been deduced on the basis of spectral and analytical data. The synthesized compounds were screened for their antimicrobial activity.

1. Introduction

Heterocycles containing sulfonamide moieties have attracted obvious attention due to their significant biological properties and their role as pharmacohores [1-6]. Studies have shown that sulfonamide compounds were used as antibacterial [7-9], antifungal [9,10], antiviral [11], anticancer [12], anti-inflammatory, analgesic [13-15], and antibacterial agents [16]. Also, a wide variety of benzimidazole derivatives have been described for their chemotherapeutic importance [17-23] and oxazole derivatives play very important role in the manufacturing process of various biologically active drugs as anticancer, antimicrobial, antidiabetic and antiobesity [24,25].

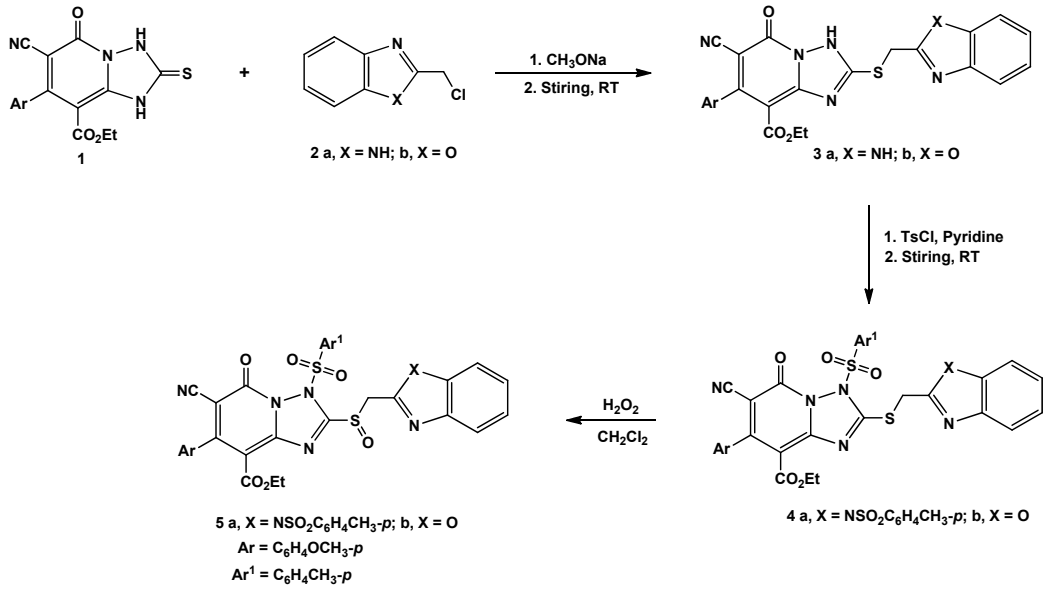
A large number of heterocyclic compounds containing pyridine rings are associated with diverse pharmacological properties such as anticancer, antimicrobial, anticonvulsant, antifungal, antiviral, anti-HIV, and anti-microbacterial activities [26,27]. The pyridine ring is one of the most well-known systems among the naturally occurring heterocycles, pyridine and fused pyridine moieties present in numerous natural products such as quinoline and isoquinoline alkaloids and nicotine and its analogs [28].

In the recent years, the biological properties of 1,2,4-triazoles have been widely investigated. They were shown to be effective as anti-inflammatory, antibacterial, anticonvulsant, dephlogisticate, anti-depressant, antifungal, anticancer, antibacterial properties, antipyretic, and antifungal agents [29-32]. Pyridyl methyl sulfinyl benzimdizole derivatives such as omeprazole, rebeprazole, lansoprazole, pantoprazole, esomptazol are the drug of choice for the acid related gastrointestinal disorders. These drugs act by inhibiting the proton pump (H/K ATPase) which involved in the acid secretion in the stomach [33].

Moreover, pyrimidine moiety have been widely used in the design of biologically active agents, structure containing such units often play an essential role owing to their wide range of biological activity particularly in cancer and virus research [34,35].

Coumarins are a structural scaffold in the numerous natural products and one of the well-known oxygen containing heterocycles showing a variety of biological applications [36-38]. As a part of our ongoing studies we now describe synthesis of new 1,2,4-triazolo[1,5-*a*]pyridine, pyrimidine sulfonamides, sulfinyl derivatives and in connection with our previous studies [39-47], on poly-functionally heteroaromatic compounds, we reported here 1,2,4-triazolo[1,5-*a*]pyridine, pyrimidine, and coumarin with benzimidazole, and/or benzooxazole moiety in single molecular framework with evaluation of their biological activities that we are expected to have enhanced biological activities which is the goal of our study.

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
http://dx.doi.org/10.5155/eurjchem.5.3.481-487.1054



Scheme 1

2. Experimental

2.1. Instrumentation

Melting points were determined on a Gallen-kamp apparatus and are uncorrected. The IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^{1}H NMR spectra were determined in DMSO-d_6 at 300 MHz on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GC/MS-QP1000 EX spectrometer at 70 Ev. Elemental analyses were carried out at the Microanalytical Center of Cairo University. Ethyl 6-cyano-7-(4-methoxyphenyl)-5-oxo-2-thioxo-1,2,3,5-tetrahydro[1,2,4]triazolo[1,5-*a*]pyridine-8-carboxylate [48] (**1**) and 2-(chloromethyl)benzimidazole or 2-(chloromethyl) benzooxazole (**2a**,**b**) were prepared according to the reported literature [49-51] (Scheme 1).

2.2. Synthesis

2.2.1. General procedure for synthesis of compounds 3a, 3b, 9 and 13

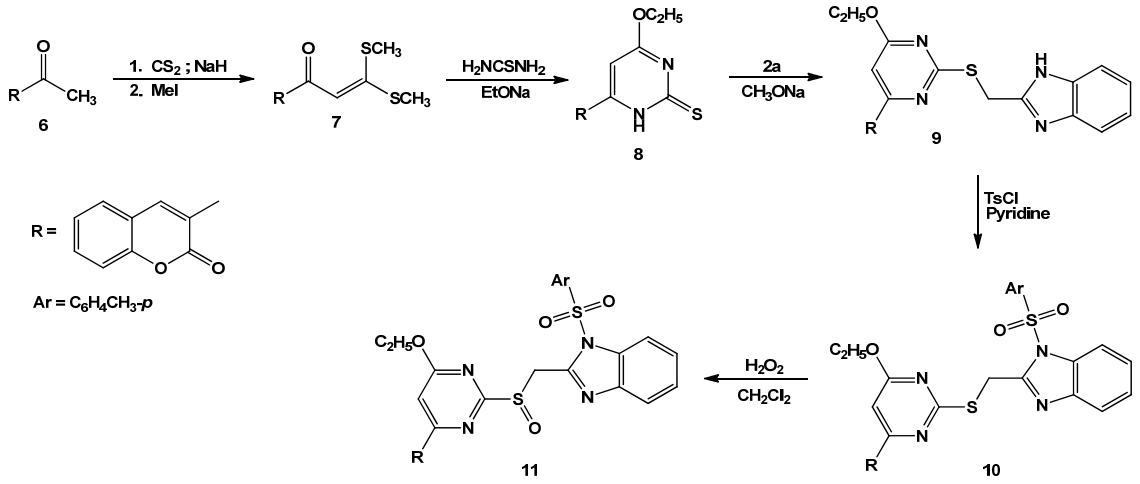
Sodium (25 mmol) was added to a solution of compound **1**, **8** and **12** (20 mmol) in anhydrous MeOH (100 mL) and the mixture was stirred vigorously for 1 h, 2-(chloromethyl) benzimidazole and/or 2-(chloromethyl)benzooxazole (**2a**,**b**) (20 mmol) was added portion-wise to the mixture and left to stirring for 3 days. The reactions mixture was triturated was ice water containing HCl. A yellow to brown precipitate was formed, filtered off and washed was water several times, dried and recrystallized from the appropriate solvent (Scheme 1-3).

Ethyl 2-((1H-benzo[d]imidazol-2-yl)methylthio)-6-cyano-3,5-dihydro-7-(4-methoxyphenyl)-5-oxo-[1,2,4]-triazolo[1,5-a] pyridine-8-carboxylate (**3a**): Recrystallized from DMF/ H_2O. Color: Brown. Yield: 69%. M.p.: 195-196 °C. FT-IR (KBr, ν, cm^{-1}): 3375, 3268 (2NH), 3115 (CH), 2905, 2850 (CH) 2212 (CN), 1685 (C=O), 1664 (C=O), 1628 (C=N), 1586 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.17 (t, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.03 (q, 2H, CH_2), 4.64 (s, 2H, SCH_2), 8.64 (s, 1H, NH, D_2O-exchangeable), 6.62 (d, 2H, Ar-*H*), 7.31 (d, 2H, Bz-*H*), 7.75 (d, 2H, Bz-*H*), 7.80 (d, 2H, Ar-H), 11.43 (s, 1H, NH, D_2O-exchangeable). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 168.8 (C-7), 167, 164.5 (2C=O), 158.9 (C-ArOCH_3-p), 152.1, 147.2 (C-triazole), 142.6 (C-imidazole), 116.4 (CN), 115.7 (C-6), 109.4 (C-8), 114.5, 115.2, 123.3, 124.7, 127.9 (C-Ar), 62.1 (CH_2), 55.8 (OCH_3), 33.4 (CH_2S), 13.8 (CH_3). MS (EI, *m/z* (%)): 500 (M$^+$, 52). Anal. calcd. for $C_{25}H_{20}N_6O_4S$: C, 59.99; H, 4.03; N, 16.79. Found: C, 59.95; H, 3.99; N, 16.73%.

Ethyl 2-((benzo[d]oxazol-2-yl)methylthio)-6-cyano-3,5-dihydro-7-(4-methoxyphenyl)-5-oxo-[1,2,4]-triazolo[1,5-a]pyridine-8-carboxylate (**3b**): Recrystallized from DMF/ H_2O. Color: Pale brown. Yield: 56%. M.p.: 182 °C. FT-IR (KBr, ν, cm^{-1}): 3263 (NH), 3119 (CH), 2910, 2846 (CH) 2204 (CN), 1689 (C=O), 1668 (C=O), 1632 (C=N); 1579 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.14 (t, 3H, CH_3), 3.78 (s, 3H, OCH_3), 4.09 (q, 2H, CH_2), 4.61 (s, 2H, SCH_2), 8.89 (s, 1H, NH, D_2O-exchangeable), 6.64-7.84 (m, 8H, Ar-*H*). MS (EI, *m/z* (%)): 501 (M$^+$, 62). Anal. calcd. for $C_{25}H_{19}N_5O_5S$: C, 59.87; H, 3.82; N, 13.96. Found: C, 59.91; H, 3.81; N, 13.94%.

3-(2-((1H-Benzo[d]imidazol-2-yl)methylthio)-6-ethoxypyrimidin-4-yl)-2H-chromen-2-one (**9**): Recrystallized from dioxane. Color: Pale yellow. Yield: 73%. M.p.: 175 °C. FT-IR (KBr, ν, cm^{-1}):3279 (NH), 3119 (CH), 2896, 2847 (CH), 1691 (C=O), 1627 (C=N); 1582 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.27 (t, 3H, CH_3), 3.82 (q, 2H, CH_2), 4.39 (s, 2H, SCH_2), 6.79 (s, 1H, H-5), 7.03-7.11 (m, 8H, Ar-*H*), 8.05 (s, 1H, H-4$_{chromen}$), 11.13 (s, 1H, NH, D_2O-exchangeable). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 169.4 (C-4$_{pyrimidine}$), 169.2 (C-2$_{pyrimidine}$), 165 (C=O), 162.7 (C-6$_{pyrimidine}$), 151.8 (C-8a $_{chromen}$), 146.5 (C-4$_{chromen}$), 143.5 (C-2$_{imidazole}$), 139.6 (C-3a, 8a$_{imidazole}$), 107.3 (C-5$_{pyrimidine}$), 128.9, 127.6, 125.7, 123.2, 121.3, 122.1, 115.5 (C-Ar), 64.1 (CH_2), 34.9 (CH_2S), 14.7 (CH_3). MS (EI, *m/z* (%)): 430 (M$^+$, 86). Anal. calcd. for $C_{23}H_{18}N_4O_3S$: C, 64.17; H, 4.21; N, 13.01. Found: C, 64.04; H, 4.16; N, 13.05%.

Ethyl 2-(((8-(ethoxycarbonyl)-6-cyano-3,5-dihydro-7-(4-methoxyphenyl)-5-oxo-[1,2,4]triazolo[1,5-a]pyridine-2-ylthio) methyl)-sulfanyl)-6-cyano-3,5-dihydro-7-(4-methoxyphenyl)-5-oxo-[1,2,4]-triazolo[1,5-a]pyridine-8-carboxylate (**13**): Recrystallized from dioxane. Color: Pale brown. Yield: 38%. M.p.: 155 °C. FT-IR (KBr, ν, cm^{-1}): 3275, 3262 (NH), 3119 (CH), 2215 (CN), 1689 (C=O), 1669 (C=O), 1635 (C=N); 1584 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.23 (t, 6H, $2CH_3$), 3.77 (s, 6H, $2OCH_3$, 4.11 (q, 4H, $2CH_2$)), 4.61 (s, 2H, SCH_2), 8.74, 8.78 (brs, 2H, 2NH, D_2O-exchangeable), 6.71-6.79 (m, 4H, Ar-*H*), 7.22-7.27 (m, 4H, Ar-*H*).



Scheme 2

MS (EI, *m/z* (%)): 752 (M^+, 15). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 167.3, 161.5 (4C=O), 153.7 (2C-$2_{triazole}$), 159.3 (2C-$ArOCH_3$-p), 152.1 (2C-7), 146.8 (2C-8a), 115.9 (2CN), 108.9 (2C-8), 128.1, 125.2, 115.4, 114.3, 109.2 (12C-Ar), 61.9 ($2CH_2$), 55.8 ($2OCH_3$), 19.7 (-SCH_2S-), 14.1 ($2CH_3$). Anal. calcd. for $C_{35}H_{28}N_8O_8S_2$: C, 55.84; H, 3.75; N, 14.89. Found: C, 55.79; H, 3.81; N, 14.86%.

2.2.2. Synthesis of 3-(3,3-bis(methylthio)acryloyl)-2H-chromen-2-one (7)

Prepared according to procedure [52], to a solution of NaH (0.45 mol) in benzene (150 mL), a solution of compound **6** (0.2 mol), CS_2 (0.2 mol) in dry DMF (100 mL) was added in portions during 1 h. The reaction mixture was kept under stirring for 3 h. followed by addition of methyl iodide (0.4 mol) in portions with cooling. The reaction mixture was allowed to stand at room temperature for 6 h. and then refluxed for further 4 h. After cooling, it pour into ice water with stirring. The precipitate obtained was filtered off and washed was cold water several times and dried (Scheme 2). Recrystallized from DMF/EtOH. Color: Buff crystals. Yield: 63%. M.p.: 92 °C. FT-IR (KBr, ν, cm^{-1}): 3114 (CH), 1697 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.35 (s, 6H, $2CH_3$), 6.21 (s, 1H, C=H), 7.09-7.35 (m, 4H, Ar-*H*), 8.43 (s, 1H, H-$4_{chromen}$). MS (EI, *m/z* (%)): 291 (M^+, 29). Anal. calcd. for $C_{14}H_{12}O_3S_2$: C, 57.51; H, 4.14. Found: C, 57.49; H, 4.04%.

2.2.3. Synthesis of 3-(6-ethoxy-2-mercaptopyrimidin-4-yl)-2H-chromen-2-one (8)

Prepared according to procedure [52], to a solution of the sodium ethoxide ((0.04 mol) of Na in 75 (mL) of EtOH) was added compound **7** (0.02 mol) and the reaction mixture was refluxed for 10-12 h. The solvent was removed under reduced pressure and the residue was treated with glacial acetic acid (15 mL) to dissolve the sodium salt of pyrimidine and refluxed for 15 min. The reaction mixture was poured on crushed ice and the precipitate was filtered off and washed was cold water several times and dried (Scheme 2). Recrystallized from DMF. Color: Brownish-yellow. Yield: 51%. M.p.: 215-217 °C. FT-IR (KBr, ν, cm^{-1}): 3145 (NH), 1165 (C=S), 3119 (CH), 1695 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.28 (t, 3H, CH_3), 4.29 (q, 2H, CH_2), 6.81 (s, 1H, H-5), 7.11-7.34 (m, 4H, Ar-*H*), 8.05 (s, 1H, H-$4_{chromen}$), 8.65 (brs, 1H, SH, D_2O-exchangeable). MS (EI, *m/z* (%)): 300 (M^+, 57). Anal. calcd. for $C_{15}H_{12}N_2O_3S$: C, 59.99; H, 4.03; N, 9.33. Found: C, 59.94; H, 4.01; N, 9.36%.

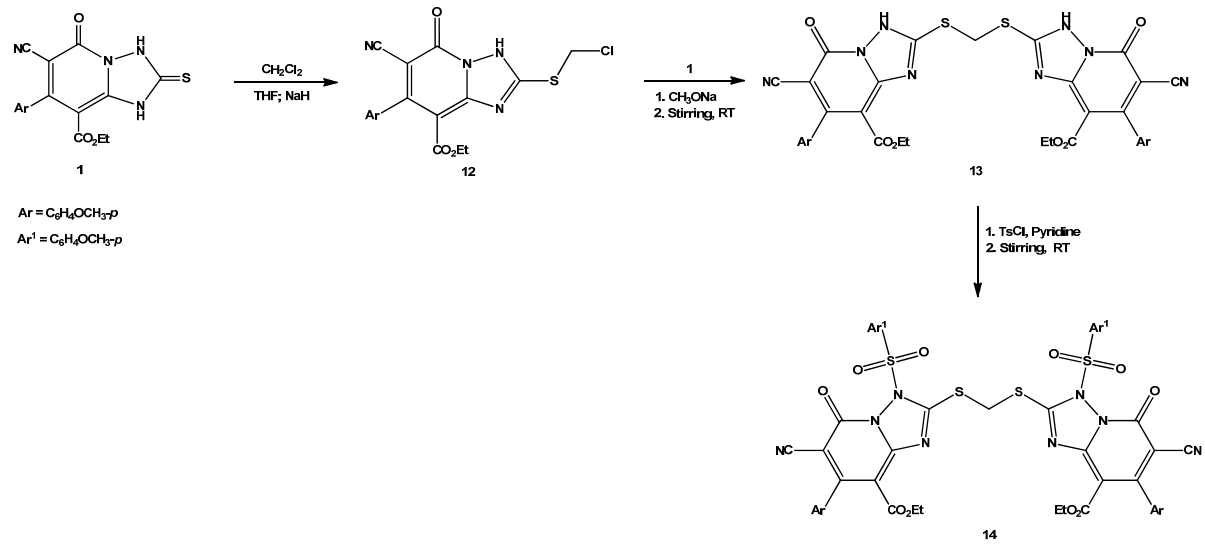
2.2.4. Synthesis of ethyl 2-((chloromethyl)thio)-6-cyano-7-(4-methoxphenyl)-5-oxo-3,5-dihydro-[1,2,4]triazolo[1,5-a] pyridine-8-carboxylate (12)

Prepared according to procedure, to a solution of compound **1** (20 mmol) in THF 50 (mL) containing catalytic amount of NaH was added CH_2Cl_2 (23 mmol) and the reaction mixture was refluxed for 6 h. The solvent was removed under reduced pressure and the reaction mixture was poured on crushed ice containing AcOH and the precipitate was filtered off and washed was cold water several times and dried (Scheme 3). Recrystallized from DMF. Color: Brown. Yield: 43%. M.p.: 225-227 °C. FT-IR (KBr, ν, cm^{-1}): 3362 (NH), 3118 (CH), 2908 (CH) 2116 (CN), 1688 (C=O), 1661 (C=O), 1630 (C=N); 1581 (C=C). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.16 (t, 3H, CH_3), 3.74 (s, 3H, OCH_3), 4.08 (q, 2H, CH_2), 4.89 (s, 2H, SCH_2), 8.64 (s, 1H, NH, D_2O-exchangeable), 6.62-7.89 (m, 4H, Ar-*H*). MS (EI, *m/z* (%)): 420 (M^++2, 33), 418 (M^+, 59.6). Anal. calcd. for $C_{18}H_{15}N_4O_4SCl$: C, 51.62; H, 3.61; N, 13.38. Found: C, 51.58; H, 3.59; N, 13.31%.

2.2.5. General procedure for synthesis of compounds 4a, 4b, 10 and 14

A solution of *p*-toluene-sulfonyl chloride (20 mmol) in pyridine (50 mL) was added dropwise to a solution of compound **3a** and **13** (10 mmol) or a solution of *p*-toluene-sulfonyl chloride (10 mmol) in pyridine (50 mL) was added drop-wise to a solution of compound **3b** and **9** (10 mmol) at 0 °C, within 6 h. The mixture was stirred at room temperature and left overnight. It was then quenched with ice-water containing HCl, and stirred for another 1 h. The precipitate obtained was filtered off and washed was methanol, cold water several times, dried and recrystallized from the appropriate solvent (Scheme 1-3).

Ethyl 2-((1-tosyl-1H-benzo[d]imidazol-2-yl)methylthio)-6-cyano-3,5-dihydro-7-(4-methoxyphenyl)-5-oxo-3-tosyl-[1,2,4]-triazolo[1,5-a]pyridine-8-carboxylate (**4a**): Recrystallized from DMF/H_2O. Color: Pale brown. Yield: 46%. M.p.: 164 °C. FT-IR (KBr, ν, cm^{-1}): 1372 (O=S=O), 3116 (CH), 2898 (CH), 2214 (CN), 1676 (C=O), 1665 (C=O), 1630 (C=N); 1370 (O=S=O), 1580 (C=C). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.21 (t, 3H, CH_3), 2.36 (brs, 6H, $2CH_3$), 3.73 (s, 3H, OCH_3), 4.21 (q, 2H, CH_2), 5.11 (s, 2H, SCH_2), 6.84-7.92 (m, 16H, Ar-*H*). MS (EI, *m/z* (%)): 808 (M^+, 37). Anal. calcd. for $C_{39}H_{32}N_6O_8S_3$: C, 57.91; H, 3.99; N, 10.39. Found: C, 57.87; H, 3.96; N, 10.37%.



Scheme 3

Ethyl 2-((benzo[d]oxazol-2-ylmethyl)thio)-6-cyano-7-(4-methoxyphenyl)-5-oxo-3-tosyl-3,5-dihydrol-[1,2,4]-triazolo[1,5-a]pyridine-8-carboxylate (**4b**): Recrystallized from DMF. Color: Brownish-yellow. Yield: 39%. M.p.: 197 °C. FT-IR (KBr, ν, cm^{-1}): 3116 ($CH_{arom.}$), 2891, 2850 (CH), 2216 (CN), 1681 (C=O), 1669 (C=O), 1635 (C=N); 1583 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.19 (t, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 4.19 (q, 2H, CH_2), 5.22 (s, 2H, SCH_2), 6.79-7.85 (m, 12H, Ar-*H*). MS (EI, *m/z* (%)): 655 (M^+, 42). Anal. calcd. for $C_{32}H_{25}N_5O_7S_2$: C, 58.62; H, 3.84; N, 10.68. Found: C, 58.58; H, 3.82; N, 10.67%.

3(2-((1-Tosyl-1H-benzo[d]imidazol-2-yl)methylthio)-6-ethoxypyrimidin-4-yl)-2H-chromen-2-one (**10**): Recrystallized from dioxane/H_2O. Color: Pale yellow crystals. Yield: 49%. M.p.: 168 °C. FT-IR (KBr, ν, cm^{-1}): 3118 (CH), 2893 (CH), 1694 (C=O), 1630 (C=N), 1180 (O=S=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.29 (t, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.89 (q, 2H, CH_2), 5.22 (s, 2H, SCH_2), 6.83 (s, 1H, H-5), 7.11-7.96 (m, 12H, Ar-*H*), 7.98 (s, 1H, H-$4_{chromen}$). MS (EI, *m/z* (%)): 584 (M^+, 19). Anal. calcd. for $C_{30}H_{24}N_4O_5S_2$: C, 61.63; H, 4.14; N, 9.58. Found: C, 61.59; H, 4.11; N, 9.55%.

Ethyl 2-(((8-(ethoxycarbonyl)-6-cyano-3,5-dihydro-7-(4-methoxyphenyl)-5-oxo-3-tosyl-[1,2,4]-triazolo[1,5-a]pyridine-2-ylthio)methyl)sulfanyl)-6-cyano-3,5-dihydro-7-(4-methoxyphenyl)-5-oxo-3-tosyl-[1,2,4]triazolo[1,5-a]pyridine-8-carboxylate (**14**): Recrystallized from DMF/H_2O. Color: Brown. Yield: 65%. M.p.: 149-151 °C. FT-IR (KBr, ν, cm^{-1}): 3119 (CH), 2855 (CH), 2218 (CN), 1683 (C=O), 1663 (C=O), 1630 (C=N); 1377 (O=S=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.24 (t, 6H, $2CH_3$), 2.36 (s, 6H, $2CH_3$), 4.18 (q, 4H, $2CH_2$), 3.75 (s, 6H, $2OCH_3$), 4.68 (s, 2H, SCH_2), 7.15-7.89 (m, 16H, Ar-*H*). Anal. calcd. for $C_{49}H_{40}N_8O_{12}S_4$: C, 55.46; H, 3.80; N, 10.56. Found: C, 55.40; H, 3.79; N, 10.53%.

2.2.6. General procedure for synthesis of compound 5a, 5b, and 11

Prepared according to procedure [53], to a solution of compound **4a**, **4b**, **10** and **14** (20 mmol) in CH_2Cl_2 (50 mL), H_2O_2 (30% *w:v*, 0.3 mL, 20 mmol in case of compound **4a**, **4b**, **9** and (0.6 mL), (40 mmol) in case of compound **14**) in AcOH (10 mL) was added dropwise. The reaction mixture was heated at 80 °C under stirring for 3-6 h. The solvent was then evaporated under reduced pressure. The residue was poured in methanol ice cold water. The precipitate obtained was filtered off and washed with cold water several times, dried and recrystallized from the appropriate solvent (Scheme 1 and 2).

2-((1-Tosyl-1H-benzo[d]imidazol-2-yl)methylsulfinyl)-6-cyano-3,5-dihydro-7-(4-methoxyphenyl)-5-oxo-3-tosyl-[1,2,4] triazolo[1,5-a]pyridine-8-yl propionate (**5a**): Recrystallized from DMF. Color: Brown. Yield: 33%. M.p.: 247-249 °C. FT-IR (KBr, ν, cm^{-1}): 3114 (CH), 2890 (CH), 2209 (CN), 1676 (C=O), 1661 (C=O), 1633 (C=N); 1583 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.26 (t, 3H, CH_3), 2.34-2.36 (brs, 6H, $2CH_3$), 3.75 (s, 3H, OCH_3), 4.23 (q, 2H, CH_2), 5.40 (s, 2H, SCH_2), 6.72-7.81 (m, 16H, Ar-*H*). MS (EI, *m/z* (%)): 824 (M^+, 8). Anal. calcd. for $C_{39}H_{32}N_6O_9S_3$: C, 56.78; H, 3.91; N, 10.19. Found: C, 56.71; H, 3.89; N, 10.17%.

2-((Benzo[d]oxazol-2-yl)methylsulfinyl)-6-cyano-3,5-dihydro-7-(4-methoxyphenyl)-5-oxo-3-tosyl-[1,2,4]-triazolo[1,5-a] pyridine-8-yl propionate (**5b**): Recrystallized from DMF. Color: Pale brown. Yield: 43%. M.p.: 243-244 °C. FT-IR (KBr, ν, cm^{-1}): 3119 (CH), 2895, 2857 (CH) 2213 (CN), 1679 (C=O), 1668 (C=O), 1631 (C=N); 1585 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.24 (t, 3H, CH_3), 2.35 (s, 3H, $2CH_3$), 3.73 (s, 3H, OCH_3), 4.21 (q, 2H, CH_2), 5.42 (s, 2H, SCH_2), 6.72-7.81 (m, 12H, Ar-*H*). MS (EI, *m/z* (%)): 671 (M^+, 16). Anal. calcd. for $C_{32}H_{25}N_5O_8S_2$: C, 57.22; H, 3.75; N, 10.43. Found: C, 57.16; H, 3.74; N, 10.41%.

3-(2-((1-Tosyl-1H-benzo[d]imidazol-2-yl)methylsulfinyl)-6-ethoxypyrimidin-4-yl)-2H-chromen-2-one (**11**): Recrystallized from DMF/EtOH. Color: Dark brown. Yield: 38%. M.p.: 205-206 °C. FT-IR (KBr, ν, cm^{-1}): 3145 (CH), 2894 (CH), 1694 (C=O), 1634 (C=N), 1583 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.3 (t, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.98 (q, 2H, CH_2), 5.55 (s, 2H, SCH_2), 6.82 (s, 1H, H-5), 7.13-7.93 (m, 12H, Ar-*H*), 8.03 (s, 1H, H-$4_{chromen}$). MS (EI, *m/z* (%)): 600 (M^+, 11). Anal. calcd. for $C_{30}H_{24}N_4O_6S_2$: C, 59.99; H, 4.03; N, 9.33. Found: C, 59.92; H, 4.0; N, 9.29%.

2.3. Biological activity

2.3.1. Tested organisms

Eight organisms are used as test organisms comprising of five bacteria (*Staphylococcus aureus, Bacillus sp., Salmonella typhi, Escherichia coli* [54,55], and *Nisseria lactmica* [56]) were obtained from Microbiology Laboratory of Faculty of Science, Qena and three fungi (*Alternaria alternata* strain HM01 [57], *Aspergillus terreus* strain HM13 [58], *Fusarium nivale* strain

HM25) were obtained from Mycology Laboratory of Faculty of Science, Aswan .The cultures of bacteria and fungi were sub-cultured on Muller-Hinton agar and C'zapek's-agar slants respectively and stored at 4 °C until required for study.

2.3.2. Antibacterial test using paper disc technique

The tested compounds (1 mg/disc) on sterile filter paper discs (0.3 mm diameter) and dried at 40 °C for 30 minutes. The prepared Muller-Hinton agar plates were on cultured with each of test bacteria 10^7 CFU/mL, and the filter paper discs were placed on each plate. The plates were incubated at 37 °C for 24 h. The zones of inhibition were measured and recorded.

2.3.3. Antifungal test using fungal growth rate technique

This activity was carried out using C'zapekes agar medium in petri dishes and mixed with each compound by a final concentration (1 mg/plate) and then inoculated in central zone with a fresh culture fungal disc of 3 mm in diameter. All plates were incubated at 28 °C. The diameters of cultures were measured in control dishes and in the treated plates containing culture medium supplemented with variable compounds and the average growth rates was measured.

3. Results and discussion

3.1. Synthesis

1,2,4-Triazolo[1,5-*a*]pyridine derivative (**3a**) were synthesized by stirring of ethyl 6-cyano-7-(4-methoxyphenyl)-5-oxo-2-thioxo-1,2,3,5-tetrahydro[1,2,4]triazolo[1,5-*a*]pyridine-8-carboxylate (**1**) with 2-(chloromethyl)benzimidazole (**2a**) in sodium methoxide. The structure of the product **3a** was assigned as ethyl 2-((1*H*-benzo[*d*]imidazol-2-yl)methylthio)-6-cyano-3,5-dihydro-7-(4-methoxyphenyl)-5-oxo-[1,2,4]triazolo-[1,5-*a*]pyridine-8-carboxylate based on the elemental analysis and spectral data which in agreement with this structure. Its IR spectrum indicate the absence of a free –SH absorption band and the appearance of absorption bands at 3375, 3268 cm^{-1} assignable to 2NH, 3115 cm^{-1} to CH, 2212 cm^{-1} to CN, 1685, 1664 cm^{-1} to CO, and 1586 cm^{-1} to C=C functions. Its ^{1}H NMR spectrum revealed the presence of three singlet signals at δ 11.43 ppm, δ 8.64 ppm, δ 4.64 ppm assignable to the $NH_{imidazole}$, $NH_{triazole}$, and SCH_2, respectively. The mass spectrum of compound **3a** showed the molecular ion at *m/z* 500 (M^+). Furthermore, the ^{13}C NMR spectrum also revealed signal at 33.4 ppm due to SCH_2 (Scheme 1).

Similarly, 2-(chloromethyl)benzooxazole (**2b**) reacted with compound **1** under the same conditions to yield compound **3b**. The structure of the product **3b** was assigned as ethyl 2-((benzo[*d*]oxazol-2-yl)methylthio)-6-cyano-3,5-dihydro-7-(4-methoxyphenyl)-5-oxo-[1,2,4]triazolo[1,5-*a*]pyridine-8-carboxylate based on the elemental analysis and spectral data which in agreement with this structure (see Experimental section).

Reaction of compound **3a** with tosyl chloride in pyridine gave the corresponding ethyl 2-((1-tosyl-1*H*-benzo[*d*]imidazol-2-yl)methylthio)-6-cyano-3,5-dihydro-7-(4-methoxyphenyl)-5-oxo-3-tosyl-[1,2,4]-triazolo[1,5-*a*]pyridine-8-carboxylate, **4a**. Its IR spectrum indicate the absence of a free 2NH absorption bands and the appearance of absorption bands at 1372 cm^{-1} assignable to SO_2, 2214 cm^{-1} to CN, and 1676, 1655 cm^{-1} to CO functions. Its ^{1}H NMR spectrum revealed the presence of singlet signal at δ 5.11 ppm assignable to SCH_2 (Scheme 1).

Similarly, reaction of compound **3b** with tosyl chloride in pyridine gave the corresponding **4b**. The structure of the product **4b** was assigned as ethyl 2-((benzo[d]oxazol-2-ylmethyl)thio)-6-cyano-7-(4-methoxyphenyl)-5-oxo-3-tosyl-3,5-dihydrol-[1,2,4]-triazolo[1,5-a]pyri-dine-8-carboxylate based on the elemental analysis and spectral data which in agreement with this structure (see Experimental section).

2-((1-Tosyl-1*H*-benzo[*d*]imidazol-2-yl)methylsulfinyl)-6-cyano-3,5-dihydro-7-(4-methoxyphenyl)-5-oxo-3-tosyl-[1,2,4]-triazolo[1,5-*a*]pyridine-8-yl propionate (**5a**) was synthesized by refluxing with stirring a solution of compound **4a** in dichloromethane and hydrogen peroxide in acetic acid. Its IR spectrum showed absorption bands at 2209 cm^{-1} assignable to CN and 1676, 1661 cm^{-1} to CO functions. Its ^{1}H NMR spectrum revealed the presence of singlet signal at δ 5.4 ppm assignable to -SCH_2. The mass spectrum of compound **5a** showed the molecular ion at *m/z* 824 (M^+) (Scheme 1).

Similarly, refluxing with stirring compound **4b** in dichloromethane and hydrogen peroxide in acetic acid yield the corresponding compound **5b**. The structure of compound **5b** was assigned as 2-((benzo[*d*]oxazol-2-yl)methylsulfinyl)-6-cyano-3,5-dihydro-7-(4-methoxyphenyl)-5-oxo-3-tosyl-[1,2,4]-triazolo[1,5-*a*]pyridine-8-yl propionate based on the elemental analysis and spectral data which in agreement with this structure (see Experimental section).

In continuation of our interest with the synthesis of fused hetero compounds [36], reaction of 3-acetyl-2*H*-chromen-3-one (**6**) with CS_2 in the presence of NaH followed by methylation with CH_3I to afford 3-(3,3-*bis*(methylthio) acryloyl)-2*H*-chromen-2-one, **7**. The ^{1}H NMR spectrum of the latter exhibited two characteristic singlet signals at δ 8.43 and 6.21 ppm for coumarine *H*-4 and =CH proton, respectively. The mass spectrum of compound **7** showed the molecular ion peak at *m/z* 293 (M^++1) corresponding to the molecular formula ($C_{14}H_{12}O_3S_2$). Reaction of compound **7** with thiourea in sodium ethoxide afforded the pyrimidine derivative, **8**. The ^{1}H NMR spectrum exhibited a broad signal at at δ 8.65 ppm for SH proton of pyrimidine and singlet signal for pyrimidine *H*-5 at δ 6.81 ppm. The mass spectrum of compound **8** showed the molecular ion peak at *m/z* 300 corresponding to the molecular formula ($C_{15}H_{12}N_2O_3S$).

Chromen-2-one derivative **9** was synthesized by stirring of 3-(6-ethoxy-2-marcaptopyrimidin-4-yl)-2*H*-chromen-2-one (**8**) with compound **2a** in sodium methoxide (Scheme 2). The structure of the product **9** was assigned as 3-(2-((1*H*-benzo[*d*]imidazol-2-yl)methylthio)-6-ethoxypyrimidin-4-yl)-2*H*-chromen-2-one based on the elemental analysis and spectral data which in agreement with this structure. Its IR spectrum indicate the absence of a free –SH absorption band and the appearance of absorption bands at 3279 cm^{-1} assignable to NH, 3119 cm^{-1} to CH and 1691 cm^{-1} to $CO_{chromen}$ functions. Its ^{1}H NMR spectrum revealed the presence of two singlet signals at δ 11.13 and 4.39 ppm assignable to the NH and SCH_2, respectively. The mass spectrum of compound **9** showed the molecular ion at *m/z* 430 (M^+).

Reaction of compound **9** with tosyl chloride in pyridine gave the corresponding 3(2-((1-tosyl-1*H*-benzo[*d*]imidazol-2-yl)methylthio)-6-ethoxypyrimidin-4-yl)-2H-chromen-2-one, **10**. The structure of the compound **10** was assigned based on the elemental analysis and spectral data. Its IR spectrum indicate the absence of a free NH absorption band of the benzimidazole and the appearance of absorption bands at 1180 cm^{-1} assignable to SO_2 and 1694 cm^{-1} to CO functions. Its ^{1}H NMR spectrum revealed the presence of two singlet signals at δ 2.35 ppm, and 5.22 ppm assignable to the methyl of tosyl and SCH_2 protons, whereas the aromatic protons appeared as multiplets and doublet signals at δ 7.11-7.96 ppm. The mass spectrum of compound **10** showed the molecular ion at *m/z* 584 (M^+) (Scheme 2).

3-(2-((1-Tosyl-1*H*-benzo[*d*]imidazol-2-yl)methylsulfinyl)-6-ethoxypyrimidin-4-yl)-2H-chromen-2-one (**11**) was synthesized by refluxing with stirring a solution of compound **10** in dichloromethane and hydrogen peroxide in acetic acid. The IR spectrum of compound **11** showed absorption bands at 3145 cm^{-1} assignable to CH and 1694 cm^{-1} to CO function.

Table 1. The antibacterial activity of compounds (1 mg/disc) *.

Compound no	*Staphylococcus aureus* Gram (+)	*Bacillus sp.* Gram (+)	*Escherichia coli* Gram (+)	*Neisseria Lactamica* Gram (+)	*Salmonella Typhi* Gram (-)
3a	+	-	-	-	-
3b	-	-	+	-	-
4a	+	-	+	-	-
9	+	+	+	+	+
13	+	-	+	+	+
5a	-	-	-	-	-
5b	-	-	+	-	-
10	+	+	+	+	+
14	+	+	+	+	+
4b	-	-	+	-	-
11	+	-	-	+	+

* "+" = active; "-" = non-active.

Table 2. Effect of the compounds (1 mg/plate) on fungal growth rate.

Compounds	*Altermaria altermata*	*Aspergillus terreus*	*Fusarium nivale*
3a	2.30	1.3	3.7
3b	3.05	1.2	3.0
4a	2.20	1.5	3.1
9	2.60	1.1	2.9
13	2.60	0.9	3.9
5a	3.40	1.3	3.8
5b	2.50	1.2	4.2
10	2.25	1.2	3.1
14	2.60	1.1	3.7
4b	2.60	1.3	4.0
11	2.60	1.1	3.1

Its ^{1}H NMR spectrum revealed the presence of singlet signal at δ 2.35 and 5.55 ppm assignable to methyl of tosyl and -CH_2S, whereas the aromatic protons appeared as multiplets signals at δ 7.13-7.93 ppm. The mass spectrum of compound **11** showed the molecular ion at *m/z* 600 (M^+) (Scheme 2).

1,2,4-Triazolo[1,5-a]pyridine-8-carboxylate derivative **12** was synthesized by refluxing of compound **1** with dichloro methane in a solution of THF containing sodium hydride as a basic catalyst (Scheme 3). The structure of the product **12** was assigned as ethyl 2-((chloromethyl)thio)-6-cyano-7-(4-methox phenyl)-5-oxo-3,5-dihydro-[1,2,4]triazolo[1,5-a]pyridine-8-carboxylate based on the elemental analysis and spectral data which in agreement with this structure. Its IR spectrum indicate the absence of a free –SH absorption band and the appearance of absorption bands at 3362 cm^{-1} assignable to NH, 3118 cm^{-1} to CH, 2116 cm^{-1} to CN, and 1688, 1661 cm^{-1} to CO functions. Its ^{1}H NMR spectrum revealed the presence of three singlet signals at δ 8.64 and 4.89 ppm, assignable to the $NH_{triazole}$, and SCH_2, respectively. The mass spectrum of compound **12** showed the molecular ion at *m/z* 420 (M+2, 33), 418 (M^+, 59.6).

Reaction of compound **12** with compound **1** in sodium methoxide with stirring afforded 1,2,4-triazolo[1,5-*a*]pyridine-8-carboxylate derivative **13** (Scheme 3). The structure of the product **13** was assigned as ethyl 2-(((8-(ethoxycarbonyl)-6-cyano-3,5-dihydro-7-(4-methoxyphenyl)-5-oxo-[1,2,4]triazolo[1,5-*a*]pyridine-2-ylthio)methyl)sulfanyl)-6-cyano-3,5-dihydro-7-(4-methoxyphenyl)-5-oxo-[1,2,4]triazolo[1,5-*a*]pyridine-8-carboxylate based on the elemental analysis and spectral data which in agreement with this structure. Its IR spectrum indicate the appearance of absorption bands at 3275 cm^{-1} assignable to NH, 3119 cm^{-1} to CH, 2215 cm^{-1} to CN, and 1689, 1669 cm^{-1} to CO functions. Its ^{1}H NMR spectrum revealed the presence of a broad singlet signal at δ 8.78 ppm assignable to $NH_{triazole}$ and singlet signal at δ 4.61 ppm to -SCH_2S-.

Reaction of compound **13** with tosyl chloride in pyridine gave the corresponding ethyl 2-(((8-(ethoxycarbonyl)-6-cyano-3,5-dihydro-7-(4-methoxyphenyl)-5-oxo-3-tosyl-[1,2,4]triazolo[1,5-*a*]pyridine-2-ylthio)methyl)sulfanyl)-6-cyano-3,5-dihydro-7-(4-methoxyphenyl)-5-oxo-3-tosyl-[1,2,4]triazolo[1,5-*a*]pyridine-8-carboxylate, **14**. Its IR spectrum indicate the absence of a free NH absorption bands and the appearance of absorption bands at 1377 cm^{-1} assignable to SO_2, 2218 cm^{-1} to CN, and 1683, 1663 cm^{-1} to CO. Its ^{1}H NMR spectrum revealed the presence of singlet signals at δ 2.36 ppm assignable to the methyl protons of tosyl, and δ 4.68 ppm to -SCH_2S- whereas the aromatic protons appeared as multiplets signals at δ 7.15-7.89 ppm (Scheme 3).

3.2. Antimicrobial studies

Only 1 mg of each compound was used to check its biological activity against bacteria (Table 1) and fungi (Table 2). The studied compounds showed biological activity with most of the tested bacteria and fungi. Compounds **9**, **10** and **14** inhibited the growth of all testes bacteria while **5a** had no activity to any studied bacterial species. The remaining compounds activity recorded less toxicity to the tested bacterial cell. These compounds almost inhibited all the studied fungi but *Aspergillus terreus* was slightly resistance.

Compounds **9**, **10**, and **14** showed inhibition zones with all studied bacteria while compound **13** inhibit four bacterial species (*S. aureus*, *S. typhi*, *E. coli* and *N. lactamica*). However 11 could inhibit *S. aureus*, *S. typhi*, and *N. lactamica*).

The compound **4a** showed less activity against studied bacteria which could inhibit only two species (*S. aureus* and *E. coli*). Compounds **3a**, **3b**, **5b** and **4b** recorded the lowest inhibition activity where the first one inhibits *S. aureus* and the last three compounds inhibit only *E. coli*. No biological activity was recorded with compound **5a**.

The toxicity of most compounds on fungal cells was slightly different from bacterial cells. Therefore, *Alternaria alternata* growth rate in control culture was (4.15 cm). This growth decreased to almost half with compound **4a**, **10** and **3a** (2.20, 2.25 and 2.3 cm), respectively. The toxicity effect slightly decrease with compounds **5b** (2.5 cm) and **9**, **13**, **14**, **4b**, and **11** (2.6 cm) while with compounds **3b** and **5a** was 3.05 and 3.40 cm, respectively (Table 2).

In case of *Aspergillus terreus* (Table 2) its growth in control culture was 1.5 cm which similar to the growth with compound **4a** (not toxic compound), whereas, slightly inhibition of the fungal growth was recorded with compound **3a**, **5a**, **4b** (1.3 cm), **3b**, **5b**, and **10** (1.2 cm). This toxicity slightly increased with compound **9**, **14**, **11** (1.1 cm), and **13** (0.9 cm).

Fusarium nivale was also sensitive to all compounds. Whereas control growth rate was 5 cm. Compounds **9** and **3b**

could inhibited the growth to 2.9 cm and 3.0 cm, respectively, while compound **4a**, **10** and **11** reduced the growth rate to 3.1 cm. The remaining compounds' toxicity on this fungal species decreased to 3.7 cm with compounds **3a** and **14**, 3.8 cm with **5a**, 3.9 cm with **13**, 4.0 cm with **4b**, and 4.2 cm with **5b**.

4. Conclusions

In the present work, several new substituted sulfonamides and sulfinyl compound derivatives were obtained by the reaction of 2-thioxo-1,2,4-triazolo[1,5-*a*]pyridine and pyrimi dinethiol derivatives with (2-chloromethyl)benzimidazole and/or (2-chloromethyl)benzooxazole. A little amount (1 mg) of compounds **9**, **10** and **14** was enough to inhibit the growth of all testes bacteria while compound **5a** had no activity to any studied bacterial species. The remaining compounds activity recorded less toxicity to the tested bacterial cell. The tested compounds almost inhibited all the studied fungi but *Aspergillus terreus* was slightly resistance.

Acknowledgement

Authors are thankful to Aswan Faculty of Science, Aswan University, Egypt for facilities.

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