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# Synthesis and Antimicrobial Evaluation of Some New 2-(5,6-Dihydro-4*H*-1,2,4-triazolo[4,3-a]benz[F]azepin-1-yl)methyl)-4-substituted Phthalazin-1(2*H*)-ones

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Starting from 4-substituted-phthalazin-1(2*H*)-one (**1**), A series of new 2-(5,6-dihydro-4*H*-1,2,4-triazolo[4,3-a]benz[f]azepin-1-yl)methyl)-4-substituted phthalazin-1(2*H*)-ones derivatives (**5**) have been synthesized. The structure of synthesized new compounds was established by spectral data and screened for their antimicrobial activities against various bacteria and fungi strains.

**Keywords: Triazole derivatives, Phthalazin, Antibacterial activity.**

## INTRODUCTION

Nitrogen-containing heterocyclic compounds are widespread in nature and their applications to biologically active pharmaceuticals, agrochemicals and functional materials are becoming more and more important[1]. Phthalazin-1(2*H*)-ones are important building blocks in the construction of new molecular systems for biologically active molecules[2-4]. The development of new and efficient methodologies for synthesis of potentially bioactive phthalazin-1(2*H*)-one derivatives is important. Phthalazin-1(2*H*)-ones are of considerable interest due to their antidiabetic[5], antiallergic[6], Vasorelaxant[7], PDE4 inhibitors[8], VEGF (vascular endothelial growth factor) receptor tyrosine kinases for the treatment of cancer[9,10], antiasthmatic agents with dual activities of thromboxane A2 (TXA2) synthetase inhibition and bronchodialation[11], herbicidal[12], like activities. A number of established drug molecules like hydralazine[13,14], budralazine[15,16], azelastine[17,18], ponalrestat[19] and zopolrestat[20] are prepared from the corresponding phthalazinones. Several ways have been reported in the literature for the synthesis of phthalazinones[21,22]. Generally, phthalazines are synthesized from either phthalic anhydride derivatives, 2-aryl-3-hydroxy-inden-1-ones or β-diketones *via* condensation with hydrazine hydrate by either heating[23] or using microwave irradiation[24]. In view of the aforementioned facts, it seemed most interesting to synthesize new phthalazinone derivatives with the aim to evaluate their antimicrobial activities.

## EXPERIMENTAL

Melting points were determined on a MEL-TEMP II melting point apparatus in open glass capillaries and are uncorrected. The infrared spectra were recorded for potassium bromide discs on a Pye-Unicam SP1025 spectrophotometer. NMR spectra were carried out at ambient temperature (about 25 ºC) with a Brucker AC-250 spectrometer or with a Varian Gemini 200 spectrometer at 250 MHz using tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were performed on a Hewlett-Packard 5995 gas chromatography-mass spectrometer system or on a Shimadzu GCMS-QP 1000 EX mass spectrometer. Homogeneity of the products and follow up of the reactions were checked by ascending thin-layer chromatography TLC on plates precoated with silica gel G (E. Merck; layer thickness 0.25 mm), used without pretreatment.

**General procedure for preparation [4-substituted-1(2*H*)-oxo-phthalazin-2-yl]acetic acid ethyl ester (2a-j):** A mixture of phthalazinone **1a-j** (0.01 mol), 5 g ethyl bromoacetate (0.03 mol) and 4.1 g potassium carbonate (0.03 mol) in 30 mL dry acetone was heated under reflux for 30 h, cooled at room temperature and poured into water. The obtained solid was filtered off and crystallized from appropriate solvent to give **2a-j**.

**[4-Phenyl-1(2*H*)-oxo-phthalazin-2-yl]acetic acid ethyl ester (2a):** m.p. 101-102 ºC; yield 66.4 %; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 1733, 1660 (2CO); MS (70 eV) *m/z* (%):308 ($M^+$, 10). Anal. calcd. (%) for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09; found (%) C, 70.19; H, 5.20; N, 9.03.

**[4-(4-Methoxyphenyl)-1(2*H*)-oxo-phthalazin-2-yl]acetic acid ethyl ester (2b):** m.p. 111-112 ºC; yield 60 %; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 1731, 1658 (2CO); MS (70 eV) *m/z* (%): 338($M^+$, 9). Anal. calcd. (%) for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28; found (%) C, 67.40; H, 5.39; N, 8.20.

**[4-(4-Chlorophenyl)-1(2*H*)-oxo-phthalazin-2-yl]acetic acid ethyl ester (2c):** m.p. 99-100 ºC; yield 61%; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 1740, 1664 (2CO); MS (70 eV) *m/z* (%): 342($M^+$, 12). Anal. calcd. (%) for $C_{18}H_{15}N_2O_3Cl$: C, 63.07; H, 4.41; Cl, 10.34; N, 8.17; found (%) C, 63.02; H, 4.45; Cl, 10.30; N, 8.14.

**[4-(3,4-Dichlorophenyl)-1(2*H*)-oxo-phthalazin-2-yl]acetic acid ethyl ester (2d):** m.p. 145-146 ºC; yield 70 %; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 1744, 1666 (2CO); MS (70 eV) *m/z* (%):377 ($M^+$, 10). Anal. calcd. (%) for $C_{18}H_{14}N_2O_3Cl_2$: C, 57.31; H, 3.74; Cl, 18.80; N, 7.43; found (%) C, 57.35; H, 3.70; Cl, 18.77; N, 7.40.

**[4-(4-(4-Chlorobenzyl)phenyl)-1(2*H*)-oxo-phthalazin-2-yl]acetic acid ethyl ester (2e):** m.p. 105-106 ºC; yield 67%; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 1736, 1659 (2CO); MS (70 eV) *m/z* (%):432 ($M^+$, 18). Anal. calcd. (%) for $C_{25}H_{21}N_2O_3Cl$: C, 69.36; H, 4.89; Cl, 8.19; N, 6.47; found (%) C, 69.39; H, 4.93; Cl, 8.18; N, 6.40.

**[4-(3-Chloro-4-methylphenyl)-1(2*H*)-oxo-phthalazin-2-yl]acetic acid ethyl ester (2f):** m.p. 107-108 ºC; yield 65%; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 1732, 1660 (2CO); MS (70 eV) *m/z* (%):356 ($M^+$, 14). Anal. calcd. (%) for $C_{19}H_{17}N_2O_3Cl$: C, 63.96; H, 4.80; Cl, 9.94; N, 7.85; found (%) C, 63.90; H, 4.84; Cl, 9.90; N, 7.81.

**[4-Mesityl -1(2*H*)-oxo-phthalazin-2-yl]acetic acid ethyl ester (2g):** m.p. 124-125 ºC; yield 66%; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 1731, 1662 (2CO); MS (70 eV) *m/z* (%):350 ($M^+$, 7). Anal. calcd. (%) for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99; found (%) C, 71.90; H, 6.37; N, 8.03.

**[4-(4-Benzylphenyl)-1(2*H*)-oxo-phthalazin-2-yl]acetic acid ethyl ester (2h):** m.p. 76-78 ºC; yield 71 %; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 1735, 1664 (2CO); MS (70 eV) *m/z* (%):398($M^+$, 19). Anal. calcd. (%) for $C_{25}H_{22}N_2O_3$: C, 75.36; H, 5.57; N, 7.03; found (%) C, 75.30; H, 5.62; N, 7.07.

**[4-(Pyridin-4-ylmethyl)phenyl)-1(2*H*)-oxo-phthalazin-2-yl]acetic acid ethyl ester (2i):** m.p. 117-118 ºC; yield 62 %; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 1741, 1665 (2CO); MS (70 eV) *m/z* (%):399 ($M^+$, 10). Anal. calcd. (%) for $C_{24}H_{21}N_3O_3$: C, 72.16; H, 5.30; N, 10.52; found (%) C, 72.10; H, 5.34; N, 10.54.

**[4-(Biphenyl-4-yl)-1(2*H*)-oxo-phthalazin-2-yl]acetic acid ethyl ester (2j):** m.p. 119-120 ºC; yield 60%; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 1731, 1658 (2CO); MS (70 eV) *m/z* (%):384 ($M^+$, 30). Anal. calcd. (%) for $C_{24}H_{20}N_2O_3$: C, 74.98; H, 5.24; N, 7.29; found (%) C, 74.96; H, 5.26; N, 7.33.

**General procedure for preparation [4-substituted-1(2*H*)-oxo-phthalazin-2-yl]acetic acid hydrazide (3a-j):** A mixture of ester **2** (0.01 mol) and 2 mL hydrazine hydrate in 50 mL absolute ethanol was refluxed for 2 h and cooled at room temperature. The resultant solid was filtered and crystallized from appropriate solvent to give **3**.

**[4-Phenyl-1(2*H*)-oxo-phthalazin-2-yl]acetic acid hydrazide (3a).** m.p. 210-211 ºC; yield 71%; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 3451, 3211 ($NHNH_2$), 1660 (CO); MS (70 eV) *m/z* (%): 294($M^+$, 43). Anal. calcd. (%) for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04; found (%) C, 65.34; H, 4.78; N, 19.08.

**[4-(4-Methoxyphenyl)-1(2*H*)-oxo-phthalazin-2-yl]acetic acid hydrazide (3b):** m.p. 235-236 ºC; yield 61%; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 3433, 3220 ($NHNH_2$), 1663 (CO); MS (70 eV) *m/z* (%): 324 ($M^+$, 10). Anal. calcd. (%) for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27; found (%) C, 62.90; H, 4.99; N, 17.20.

**[4-(4-Chlorophenyl)-1(2*H*)-oxo-phthalazin-2-yl]acetic acid hydrazide (3c):** m.p. 254-255 ºC; yield 63%; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 3450, 3220 ($NHNH_2$), 1664 (CO); MS (70 eV) *m/z* (%): 328 ($M^+$, 15). Anal. calcd. (%) for $C_{16}H_{13}N_4O_2Cl$: C, 58.45; H, 3.99; Cl, 10.78; N, 17.04; found (%) C, 58.40; H, 3.94; Cl, 10.79; N, 17.08.

**[4-(3,4-Dichlorophenyl)-1(2*H*)-oxo-phthalazin-2-yl]acetic acid hydrazide (3d):** m.p. 260-261 ºC; yield 68%; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 3444, 3231 ($NHNH_2$), 1667 (CO); MS (70 eV) *m/z* (%): 363 ($M^+$, 11). Anal. calcd. (%) for $C_{16}H_{12}N_4O_2Cl_2$: C, 52.91; H, 3.33; Cl, 19.52; N, 15.43; found (%) C, 52.98; H, 3.30; Cl, 19.55; N, 15.40.

**[4-(4-(4-Chlorobenzyl)phenyl)-1(2*H*)-oxo-phthalazin-2-yl]acetic acid hydrazide (3e):** m.p. 244-245 ºC; yield 66%; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 3459, 3210 ($NHNH_2$), 1661 (CO); MS (70 eV) *m/z* (%):418 ($M^+$, 10). Anal. calcd. (%) for $C_{23}H_{19}N_4O_2Cl$: C, 65.95; H, 4.57; Cl, 8.46; N, 13.38; found (%) C, 65.90; H, 4.59; Cl, 8.46; N, 13.41.

**[4-(3-Chloro-4-methylphenyl)-1(2*H*)-oxo-phthalazin-2-yl]acetic acid hydrazide (3f):** m.p. 271-272 ºC; yield 70%; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 3450, 3238 ($NHNH_2$), 1658 (CO); MS (70 eV) *m/z* (%):342 ($M^+$, 12). Anal. calcd. (%) for $C_{17}H_{15}N_4O_2Cl$: C, 59.57; H, 4.41; Cl, 10.34; N, 16.34; found (%) C, 59.50; H, 4.45; Cl, 10.38; N, 16.39.

**[4- Mesityl -1(2*H*)-oxo-phthalazin-2-yl]acetic acid hydrazide (3g):** m.p. 227-228 ºC; yield 69 %; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 3466, 3219 ($NHNH_2$), 1662 (CO); MS (70 eV) *m/z* (%):336 ($M^+$, 20). Anal. calcd. (%) for $C_{19}H_{20}N_4O_2$: C, 67.84; H, 5.99; N, 16.66; found (%) C, 67.88; H, 5.94; N, 16.60.

**[4-(4-Benzylphenyl)-1(2*H*)-oxo-phthalazin-2-yl]acetic acid hydrazide (3h):** m.p. 130-132 ºC; yield 65 %; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 3467, 3243 ($NHNH_2$), 1665 (CO); MS (70 eV) *m/z* (%):384 ($M^+$, 13). Anal. calcd. (%) for $C_{23}H_{20}N_4O_2$: C, 71.86; H, 5.24; N, 14.57; found (%) C, 71.80; H, 5.29; N, 14.53.

**[4-(Pyridin-4-ylmethyl)phenyl)-1(2*H*)-oxo-phthalazin-2-yl]acetic acid hydrazide (3i).** m.p. 130-131 ºC; yield 62 %; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 3461, 3210 ($NHNH_2$), 1660 (CO); MS (70 eV) *m/z* (%):385 ($M^+$, 18). Anal. calcd. (%) for $C_{22}H_{19}N_5O_2$: C, 68.56; H, 4.97; N, 18.17; found (%) C, 68.59; H, 4.90; N, 18.19.

**[4-(Biphenyl-4-yl)-1(2*H*)-oxo-phthalazin-2-yl]acetic acid hydrazide (3j):** m.p. 250-251 ºC; yield 77 %; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 3450, 3221 ($NHNH_2$), 1660 (CO); MS (70 eV) *m/z* (%):370 ($M^+$, 29). Anal. calcd. (%) for $C_{22}H_{18}N_4O_2$: C, 71.34; H, 4.90; N, 15.13; found (%) C, 71.34; H, 4.90; N, 15.13.

**General procedure for preparation 2-((5,6-dihydro-4*H*-1,2,4-triazolo[4,3-*a*]-benz[*f*]azepin-1-yl) methyl)-4-substituted-phthalazin-1(2*H*)-one (5a-j):** A mixture of hydrazide **3** (0.01 mol) and seven-membered lactim ether **4** (0.01 mol) in 40 mL absolute ethanol was refluxed for 5 h and cooled at room temperature. The resultant solid was filtered and crystallized from appropriate solvent to give **5a-j**.

**2-((5,6-Dihydro-4*H*-1,2,4-triazolo[4,3-*a*]benz[*f*]-azepin-1-yl) methyl)-4- phenyl -phthalazin-1(2*H*)-ones (5a):** m.p. 149-150 ºC; yield 61 %; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 1660 (CO); MS (70 eV) *m/z* (%): 419 ($M^+$, 19). Anal. calcd. (%) for $C_{26}H_{21}N_5O$: C, 74.44; H, 5.05; N, 16.70; found (%) C, 74.48; H, 5.00; N, 16.73.

**2-((5,6-Dihydro-4*H*-1,2,4-triazolo[4,3-*a*]benz[*f*]-azepin-1-yl) methyl)-4-(4-methoxyphenyl)phthalazin-1(2*H*)-ones(5b):** m.p. 130-131 ºC; yield 55 %; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 1658 (CO); MS (70 eV) *m/z* (%):449 ($M^+$, 10). Anal. calcd. (%) for $C_{27}H_{23}N_5O_2$: C, 72.14; H, 5.16; N, 15.58; found (%) C, 72.10; H, 5.15; N, 15.60.

**2-((5,6-Dihydro-4*H*-1,2,4-triazolo[4,3-*a*]benz[*f*]-azepin-1-yl) methyl)-4-(4-chlorophenyl)phthalazin-1(2*H*)-ones(5c):** m.p. 119-120 ºC; yield 56 %; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 1664 (CO); MS (70 eV) *m/z* (%):453 ($M^+$, 11). Anal. calcd. (%) for $C_{26}H_{20}N_5OCl$: C, 68.80; H, 4.44; Cl, 7.81; N, 15.43; found (%) C, 68.82; H, 4.40; Cl, 7.85; N, 15.40.

**2-((5,6-Dihydro-4*H*-1,2,4-triazolo[4,3-*a*]benz[*f*]-azepin-1-yl)methyl)-4-(3,4-dichlorophenyl)phthalazin-1(2*H*)-ones(5d):** m.p. 177-178 ºC; yield 60 %; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 1666 (CO) ; MS (70 eV) *m/z* (%): 488 ($M^+$, 14). Anal. calcd. (%) for $C_{26}H_{19}N_5OCl_2$: C, 63.94; H, 3.92; Cl, 14.52; N, 14.34; found (%) C, 63.90; H, 3.94; Cl, 14.52; N, 14.30.

**2-((5,6-Dihydro-4*H*-1,2,4-triazolo[4,3-*a*]benz[*f*]azepin-1-yl)methyl)-4-(4-(4-chlorobenzyl)phenyl)-phthalazin-1(2*H*)-ones (5e):** m.p. 120-121 ºC; yield 54 %; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 1660 (CO); MS (70 eV) *m/z* (%):543($M^+$, 9). Anal. calcd. (%) for $C_{33}H_{26}N_5OCl$: C, 72.85; H, 4.82; Cl, 6.52; N, 12.87; found (%) C, 72.80; H, 4.85; Cl, 6.50; N, 12.89.

**2-((5,6-Dihydro-4*H*-1,2,4-triazolo[4,3-*a*]benz[*f*]azepin-1-yl) methyl)-4-(3-chloro-4-methyl phenyl)phthalazin-1(2*H*)-ones (5f):** m.p. 157-158 ºC; yield 56 %; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 1665 (CO); MS (70 eV) *m/z* (%):467 ($M^+$, 8). Anal. calcd. (%) for $C_{27}H_{22}N_5OCl$: C, 69.30; H, 4.74; Cl, 7.58; N, 14.97; found (%) C, 69.39; H, 4.70; Cl, 7.57; N, 14.90.

**2-((5,6-Dihydro-4*H*-1,2,4-triazolo[4,3-*a*]benz[*f*]azepin-1-yl) methyl)-4-mesityl-phthalazin-1(2*H*)-ones (5g):** m.p. 123-124 ºC; yield 56 %; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 1663 (CO); MS (70 eV) *m/z* (%):461 ($M^+$, 12). Anal. calcd. (%) for $C_{29}H_{27}N_5O$: C, 75.46; H, 5.90; N, 15.17; found (%) C, 75.49; H, 5.93; N, 15.19.

**2-((5,6-Dihydro-4*H*-1,2,4-triazolo[4,3-*a*]benz[*f*]azepin-1-yl) methyl)-4-(4-benzylphenyl)phthalazin-1(2*H*)-ones (5h):** m.p. 100-101 ºC; yield 61%; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 1657 (CO); MS (70 eV) *m/z* (%):509 ($M^+$, 15). Anal. calcd. (%) for $C_{33}H_{27}N_5O$: C, 77.78; H, 5.34; N, 13.74; found (%) C, 77.81; H, 5.34; N, 13.78.

**2-((5,6-Dihydro-4*H*-1,2,4-triazolo[4,3-*a*]benz[*f*]azepin-1-yl)methyl)-4-(pyridin-4-ylmethyl)phenyl)phthalazin-1(2*H*)-ones (5i):** m.p. 144-145 ºC; yield 55 %; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 1661 (CO); MS (70 eV) *m/z* (%):510($M^+$, 14). Anal. calcd. (%) for $C_{32}H_{26}N_6O$: C, 75.27; H, 5.13; N, 16.46; found (%) C, 75.20; H, 5.18; N, 16.48.

**2-((5,6-Dihydro-4*H*-1,2,4-triazolo[4,3-*a*]benz[*f*]azepin-1-yl) methyl)-4-(biphenyl-4-yl)phthalazin-1(2*H*)-ones (5j):** m.p. 153-154 ºC; yield 60 %; $^1$H NMR (DMSO-$d_6$) δ: 4.91 (s, 2H, $CH_2$), 7.01-8.23 (m, 14H, Ar-H); IR (KBr, $\nu_{max}$, cm$^{-1}$): 1666 (CO); MS (70 eV) *m/z* (%):495 ($M^+$, 10). Anal. calcd. (%) for $C_{32}H_{25}N_5O$: C, 77.56; H, 5.08; N, 14.13; found (%) C, 77.50; H, 5.09; N, 14.18.

**Antibacterial:** The biological activity of the newly synthesized compounds **5a-j** were assessed against *Escherichia coli, Staphylococcus aureus, Bacillus subtilis, Salmonella typhi* bacterial strains and *Aspergillums niger* and *Candida albicans* fungal strains in term of disk diffusion method. As described in previous work[25]. Amoxicillin and ketoconazole were utilized as standard drugs for the bacteria and fungi, respectively. Initially, a screening of phthalazine-derivatives and standard drugs was accomplished at definite concentrations; 500 µg/mL. The results was documented by calculating the inhibition zone diameter at the end of 24 h for bacteria incubation and 72 h for fungi as well. Each trial was repeated twice. Based on the obtained results, the minimum inhibitory concentration (MIC) of compounds; **5a-j** against all bacterial and fungal strains was further investigated by liquid dilution method as described by El-Hashash *et al.*[25], in which "stock solutions of the target compounds of 500, 250, 200, 100, 62.5, 50, 25 and 12.5 µg mL$^{-1}$ concentrations were mixed with DMSO as solvent". Solutions of amoxicillin and ketoconazole, which considered as standard drugs were arranged at the same concentrations. Cultures of both bacteria and fungi were also prepared prior

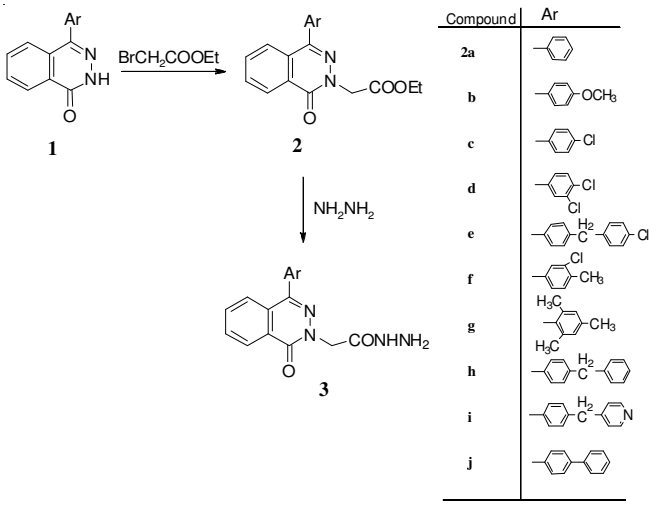
to the main test. Then, in a test tube series; 1 mL of phthalazine compound solution; different concentrations together with 0.2 mL of bacteria/fungi was added. To the last solutions, 3.8 mL of sterile distilled water was added to each of the previous test tubes. All tubes were left for incubation at 37 °C for 24 h. The observed turbidity obtained is representing the growth of both bacteria and fungi. This technique was repeated, for comparison by altering the phthalazine compounds with amoxicillin and ketoconazole. The minimum inhibitory concentration, at which there is no growth, was detected as the MIC value (Table-1). The comparison between the MICs (in µg/mL) for the powerful compounds and standard drugs against all tested microorganisms are represented in the Table-1.

## RESULTS AND DISCUSSION

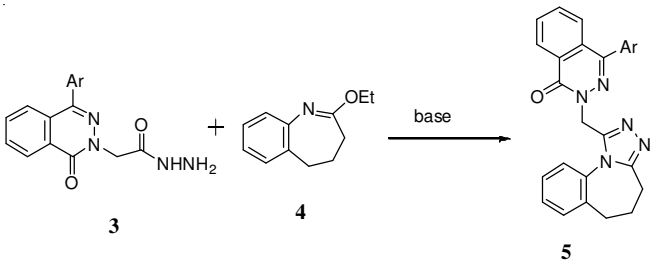
The target compound [4-substituted-1(2*H*)-oxo-phthalazin-2yl] acetic acid hydrazide **(3)** in the present study was readily obtained by the reaction of phthalazine acetic acid ethyl ester **2** with hydrazine hydrate, which in was turn prepared from 4-substituted-phthalazin-1(2*H*)-one **(1)**.

The structure of compounds **2a-j** was confirmed on the basis of their elemental analysis and spectral data. The IR spectrum showed a characteristic absorption band at ν = 1742-1733 $cm^{-1}$ corresponding to CO of ester, CO of cyclic amide at ν = 1665-1658 $cm^{-1}$ and devoid any band for NH. The $^1H$ NMR spectrum of compound **2a-j** showed a triplet signal at δ 1.33-1.48 assigned for $CH_3CH_2$, a quartet signal at 4.13-4.22 assigned for $CH_2CH_3$, a singlet at 4.70-4.82 assigned for $CH_2CO$. The hydrazide derivative **3a-j** revealed absorption bands at ν = 3188-3162 and 3458-3308 $cm^{-1}$ corresponding to $NHNH_2$ groups. The $^1HNMR$ spectrum of compound **5c** showed δ = 4.43 (s, 2H, $NH_2$ exchangeable with $D_2O$), 4.74 (s, 2H, $CH_2CO$), 9.3 (s, 1H, NH exchangeable with $D_2O$) ppm and aromatic protons.

Cyclocondensation of hydrazide derivatives **3a-j** with seven-membered lactim ether **4** afforded the corresponding 5,6-dihydro-4*H*-1,2,4-triazolo[4,3-a]benz[f]azepine derivatives **5a-j**. The structure of the tricycles **5** was confirmed on the basis of their elemental analysis and spectral data. The IR spectrum revealed no absorption for $NHNH_2$ groups. The features of the $^1H$ NMR spectrum include very broad signals




for the methylene protons in the seven-membered ring: 2.05-2.18 (2H, 5-H); 2.30-2.39 ppm (2H, 4-H) and two equal intensity, broad signals at 2.66-2.76 and 2.95-3.11 ppm (each 1H, 6-H). The $^{13}C$ NMR spectrum of compound **5a-j** agrees well with the proposed structure.




### Conclusion

We reported here the successful synthesis of different 2-((5,6-dihydro-4*H*-1,2,4-triazolo[4,3-*a*]benz[*f*]azepin-1-yl) methyl)-4-substituted-phthalazin-1(2*H*)-ones. Most of the newly synthesized compounds were tested for their antimicrobial and antiinflammatory activity. The antimicrobial activity study revealed that all the compounds tested showed moderate to good antibacterial and antifungal activities against pathogenic strains. In case of antiinflammatory activity, compounds showed good activity among the tested compounds.

TABLE-1
ANTIMICROBIAL ACTIVITY OF COMPOUNDS **5a-j**

| Compounds | Minimum inhibitory concentration (MIC) in µg/mL | | | | | |
|---|---|---|---|---|---|---|
| | Bacterial strains | | | | Fungal strains | |
| | *S. aureus* | *B. subtilis* | *S. typhi* | *E. coli* | *A. niger* | *C. albican* |
| **5a** | 250 | 250 | 500 | 500 | – | 500 |
| **5b** | – | 500 | – | – | 500 | – |
| **5c** | 100 | 50 | 50 | 100 | 250 | 500 |
| **5d** | 25 | 25 | 25 | 25 | 125 | 62.5 |
| **5e** | 25 | 25 | 25 | 50 | 62.5 | 62.5 |
| **5f** | 25 | 50 | 50 | 50 | 125 | 125 |
| **5g** | 25 | 50 | 25 | 25 | 62.5 | 125 |
| **5h** | 250 | – | – | 500 | 250 | – |
| **5i** | 50 | 25 | 25 | 25 | 62.5 | 125 |
| **5j** | 500 | 500 | – | 200 | – | 500 |
| Amoxicillin | 6.25 | 6.25 | 6.25 | 6.25 | – | – |
| Ketaconazole | – | – | – | – | 31.25 | 31.25 |

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