Med Chem Res
DOI 10.1007/s00044-016-1629-4

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Regioselective one pot synthesis of 1,2,3-triazole derivatives bearing phthalazine moiety and their pharmacological activity

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Received: 29 January 2015 / Accepted: 27 June 2016
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Abstract A new series of phthalazine-based 1,2,3-triazole derivatives (**5a–h**, **6a–f** and **7a–d**) were synthesized from the corresponding 2-(4-methyl/chloro benzyloxy) benzoic acid by multi-step reactions. Synthesized compounds were characterized by spectral studies and C, H, N analysis. The final compounds were screened for their antimicrobial, antifungal and antioxidant activity. Among them compounds **5c**, **5g**, **5h**, **6b** and **6e** showed good antibacterial activity as compared to the standard drug streptomycin, whereas compounds **5g** and **6d** showed good antifungal activity comparable to the standard drug Fluconazole. Compounds **5a**, **5f** and **7c** showed significant antioxidant property when compared with the standard butylated hydroxytoluene.

Keywords Phthalazine · 1,2,3, Triazole · Click chemistry · Antimicrobial activity · Antioxidant activity

Electronic supplementary material The online version of this article (doi:10.1007/s00044-016-1629-4) contains supplementary material, which is available to authorized users.

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Introduction

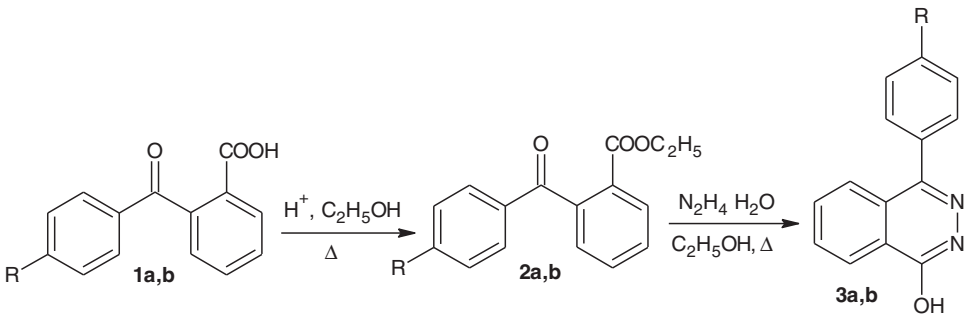
Synthesis of new heterocyclic derivatives and screening their pharmacological activities are the major target in the present day research senario. Now a days microbial stains are getting more resistant towards the existing drugs and it is a challenge to the synthetic chemists to replace the less-active drugs with newer molecules that are more effective with different mode of action. Phthalazines are an important class of nitrogen heterocycles that possess various biological activities. Phthalazines have been reported to possess antimicrobial activitiy as shown in literature (Joshi et al., 2000, Chung-Kyu et al., 2007, Khalil et al., 2009, Sridhara et al., 2010, Maher et al., 2012, Ibrahim et al., 2014.

In recent years, regioselective click chemistry has become popular in the synthetic organic and biomedicinal chemistry. Synthesis of 1,2,3-triazoles by the reaction of azides and terminal alkynes is well known and in presence of Copper(I) catalyst, the reaction is highly regiospecific and exclusively gives 1,4-disubstituted 1,2,3-triazoles (Vsevolod et al., 2002). Literature reveals that 1,2,3-triazoles are highly privileged structure and the derivatives of which exhibit excellent biological activities such as antimicrobial (Ashok et al., 2014; Zhao et al., 2012; Thomas et al., 2010), antitubercular (Rama et al., 2010), anticancer (Hichem et al., 2013), antiviral (Aurelien et al., 2011), antiepileptic (Ulloora et al., 2013) etc.

Prompted by these observations and in continuation of our search on biologically active heterocycles, we hereby report the synthesis of some new 1,2,3-triazole derivatives bearing phthalazine moiety via click chemistry approach. The new compounds so synthesized were screened for its antimicrobial activity and antioxidant activity (Schemes 1, 2).

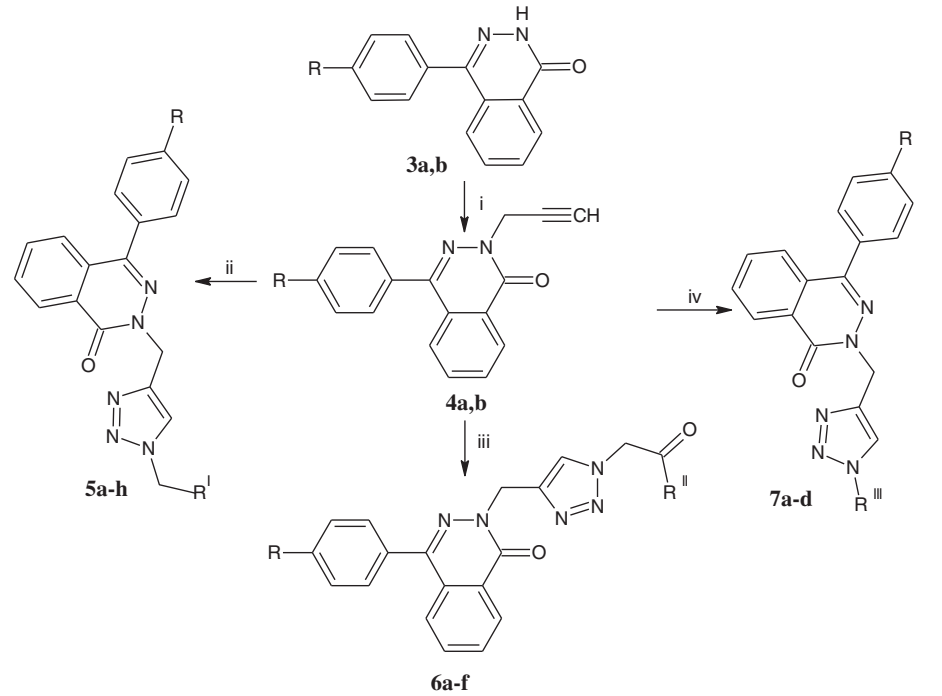
Published online: 11 August 2016

Scheme 1 Synthetic route for 4-(4-chloro/methylphenyl) phthalazin-1-ol (**3a, b**)



Where R= CH_3, Cl

Scheme 2 Synthetic route for1-[(1-substituted-1*H*-1,2,3-triazol-4-yl)methoxy]-4-(4-chloro/methylphenyl) phthalazine (**5a–h**, **6a–f** and **7a–d**)



Where R= CH_3, Cl

R^{I}= 3-methylphenyl, 4-nitrophenyl, 2,4-dichlorophenyl, phenyl

R^{II}= 4-methylphenyl, 4-hydroxyphenyl, 2,4-dichlorophenyl

R^{III} = Isopropyl, allyl

(i) Propargyl bromide, K_2CO_3, DMF, 65 °C, 2 h. (ii, iii and iv) benzyl, phenacyl and alkyl bromide, NaN_3, aqueous PEG 400 (10 mL, 1:1, v/v), sodium ascorbate, 10 mol % of $CuSO_4$ $5H_2O$, RT, 10-16hrs.

Experimental

Analysis and instruments

Melting points were determined by open capillary method and were uncorrected. The IR spectra (in KBr pellets) were recorded on a JASCO FT/IR-4100 spectrophotometer. ^{1}H-NMR and ^{13}C NMR spectra were recorded (dimethyl-sulphoxide (DMSO)-d_6, $CDCl_3$) on a Bruker (400, 100 MHz) instrument using TMS as internal standard. Chemical shift values are given in δ (ppm) scales. The mass spectra were recorded on a JEOL JMS-D 300 mass spectrometer

operating at 70 eV. Elemental analyses were performed on a Flash EA 1112 series CHNS-O Analyzer. The completion of the reaction was checked by thin layer chromatography (TLC) on silica gel coated aluminium sheets (silica gel 60 F254) obtained from Merck. Commercial grade solvents were used and reagents were purchased from S. D. Fine chemicals-India. 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging assay was performed on a Shimadzu UV-1800, UV-visible spectrophotometer.

*Synthesis of 4-(4-chloro/methylphenyl)phthalazin-1-ol (**3a, b**)*

2-(4-chloro/methylbenzoyl)benzoic acid (**1**) (0.1 mol) is refluxed in ethanol (25 mL) for 5 h in presence of catalytic amount of sulphuric acid. After the completion of reaction ethanol is distilled out, the ester is dissolved in ethyl acetate and washed with 5 % sodium bicarbonate solution followed by water wash. Ethyl acetate layer is concentrated to get the crude ethyl 2-(4-chloro/methylbenzoyl)benzoate **2a, b.** The ethyl 2-(4-chloro/methylbenzoyl)benzoate **2a, b** was further refluxed with hydrazine hydrate (5 mL, 98 %) in absolute ethanol (50 mL) with one or two drops of sulphuric acid for 2 h. Solid separated on cooling was filtered off, washed with little chilled ethanol and dried to give **3a, b** (Desai and Desai, 1980). The product was taken as such for next stage reaction without further purification.

*Syntheses of 4-(4-chloro/methylphenyl)-2-prop-2-yn-1-ylphthalazin-1(2H)-one (**4a, b**)*

A mixture of 4-(4-chloro/methylphenyl)phthalazin-1-ol (**3a**, **b**) (0.015 mol), anhydrous potassium carbonate (3.04 g 0.022 mol) and propargylbromide (1.78 g, 0.015 mol) in DMF (25 mL) was stirred at 65 °C for 2 h. The completion of reaction was monitored by TLC. The reaction mixture was poured into ice-cold water. The solid product obtained was purified by column chromatography using n-hexane and ethyl acetate mixture as eluent to get pure compound.

*4-(4-methylphenyl)-2-prop-2-yn-1-ylphthalazin-1(2H)-one (**4a**)*

Yield: 73 %; white microcrystals; mp: 168–170 °C. IR (KBr ν_{max}/cm^{-1}): 2951 (C–H–str), 2215 (C≡C), 1657 (C=O), 1117 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3), 3.32 (s, 1H, C≡CH), 4.97 (s, 2H, N–CH_2), 7.37 (d, 2H, ArH, J =8 Hz), 7.48 (d, 2H, ArH, J =8 Hz), 7.71 (1H, ArH), 7.91 (2H, ArH), 8.36 (1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 20.89 (CH_3), 40.30(N–CH_2), 74.95 (acetylenic C), 79.01(acetylenic C), 126.51(C-5 of phthalazine), 126.85(C-8 of phthalazine), 127.30(C-2 of 4-methylbenzene), 128.68(C-9 of phthalazine), 129.12, (C-1 of 4-methylbenzene), 129.28 (C-10 of phthalazine), 131.56 (C-3 of 4-methylbenzene), 132.11 (C-7 of phthalazine), 133.79 (C-6 of phthalazine), 138.79 (C-4 of 4-methylbenzene), 146.73 (C-4 of phthalazine), 157.48(CO, C-1 of phthalazine); . LC–MS (m/z): 275 (M + 1, 100 %); Anal. calcd. For $C_{18}H_{14}N_2O$; Calcd: C, 78.81; H, 5.14; N, 10.21; found: C, 78.83; H, 5.14; N, 10.20.

*4-(4-chlorophenyl)-2-prop-2-yn-1-ylphthalazin-1(2H)-one (**4b**)*

Yield: 65 %; Yellowish microcrystals; mp: 146–148 °C. IR (KBr ν_{max}/cm^{-1}): 2948 (C–H–str), 2220 (C≡C),1650 (C=O), 1111 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.30 (s, 1H, C≡CH), 4.95 (s, 1H, N–CH_2), 7.57 (d, 2H, ArH), 7.65 (d, 2H, ArH), 7.70 (1H, ArH), 7.91 (2H, ArH), 8.36 (1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 40.33 (N–CH_2), 74.91 (acetylenic C), 78.91(acetylenic C), 126.51 (C-5 of phthalazine), 126.95 (C-8 of phthalazine), 127.95 (C-9 of phthalazine), 128.98 (C-3 of 4-chlorobenzene), 129.12 (C-1 of 4-chlorobenzene), 131.76 (C-10 of phthalazine), 132.51 (C-2 of 4-chlorobenzene), 133.79 (C-7 of phthalazine), 134.29 (C-6 of phthalazine), 134.53 (C-4 of 4-chlorobenzene), 146.71 (C-4 of phthalazine), 157.48 (CO); LC–MS (m/z): 295 (M + 1, 100 %); Anal. calcd. For $C_{17}H_{11}ClN_2O$; Calcd: C, 69.28; H, 3.76; N, 12.03; found: C, 69.29; H, 3.78; N, 12.01.

*General procedure for the syntheses of 2-{[1-(alkyl/4-substitutedbenyl/benzoyl)-1H-1,2,3-triazol-4-yl]methyl}-4-(4-chloro/methylphenyl)phthalazin-1(2H)-one (**5a–h**, **6a–f** and **7a–d**)*

To a stirred solution of alkyl bromide (benzyl, phenacyl or alkyl/alkenyl) (0.50 g, 0.0015 mol) and sodium azide (0.12 g, 0.0018 mol) in aqueous PEG 400 (polyethylene glycol) (10 mL, 1:1, v/v), 4-(4-chloro/methylphenyl)-2-prop-2-yn-1-ylphthalazin-1(2*H*)-one (**4a**, **b**) (0.0015 mol), sodium ascorbate (0.356 g, 0.0015 mol) and 10 mol % of copper sulphate were added. The heterogeneous mixture was stirred vigorously overnight (12 h). Completion of the reaction was monitored by TLC. The product was then extracted with ethyl acetate and concentrated. The crude product was recrystallized from ethyl acetate to get the pure compound.

*2-{[1-(3-Methylbenzyl)-1H-1,2,3-triazol-4-yl]methyl}-4-(4-methylphenyl)phthalazin-1(2H)-one (**5a**)*

White microcrystals; Yield: 82 % ; mp: 198–200 °C; IR (KBr) ν_{max}: 2976, 1660, 1320 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.24 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 5.41 (s, 2H, CH_2), 5.49 (s, 2H, CH_2), 7.09 (m, 3H, ArH), 7.22 (m, 1H, ArH), 7.34 (d, 2H, ArH, J = 8 Hz), 7.44 (d, 2H, ArH, J = 8 Hz), 7.69–7.71 (m, 1H, ArH), 7.89–7.91 (m, 2H, ArH), 8.35 (s, 1H, 1,2,3-triazole H), 8.37 (m,1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 20.88 (CH_3), 46.16 (N–CH_2),

52.72 (N–CH_2), 123.86 (C-5 of triazole), 125.05 (C-5 of phthalazine), 126.51 (C-8 of phthalazine), 126.70 (C-4 of 3-methylbenzene), 127.47 (C-6 of 3-methylbenzene), 128.51 (C-2 of 4-methylbenzene, C-2 of 3-methylbenzene), 128.60 (C-9 of phthalazine), 128.71 (C-5 of 3-methylbenzene), 129.07 (C-1 of 4-methylbenzene), 129.28 (C-10 of phthalazine), 131.72 (C-3 of 4-methylbenzene), 131.93 (C-7 of phthalazine), 133.61 (C-6 of phthalazine), 135.92 (C-3 of 3-methylbenzene), 137.91 (C-1 of 3-methylbenzene),138.68 (C-4 of 4-methylbenzene), 143.00 (C-4 of triazole), 146.36 (C-4 of phthalazine),157.82 (CO, C-1 of phthalazine); LC–MS (m/z): 422 ($M+1$, 100 %); Anal. calcd. For $C_{26}H_{23}N_5O$; Calcd: C, 74.09; H, 5.50; N, 16.62; found: C, 74.07; H, 5.51; N, 16.63.

*2-{[1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl]methyl}-4-(4-methylphenyl)phthalazin-1(2H)-one (**5b**)*

Pale yellow microcrystals; Yield: 77 %; mp: 140–142 °C; IR (KBr ν_{max}/cm^{-1}): 2960 (C–H–str), 1661 (C=O), 1304 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.1 (s, 3H, CH_3), 5.52 (s, 2H, CH_2), 5.81(s, 2H, CH_2), 7.27 (d,2H, ArH), 7.34 (d, 2H, ArH), 7.69–7.78 (m, 4H, ArH), 7.95 (m, 2H, ArH), 8.27–8.31 (m, 2H, ArH), 8.38 (1H, 1,2,3-triazole H); ^{13}C NMR (100 MHz, DMSO-d_6): 21.52 (CH_3), 46.70 (N–CH_2), 52.25 (N–CH_2), 124.40 (C-3 of 4-nitrobenzene), 125.01(C-5 of triazole), 126.12 (C-5 of phthalazine), 127.03 (C-8 of phthalazine), 127.25 (C-2 of 4-nitrobenzene), 127.98 (C-2 of 4-methylbenzene), 129.12 (C-9 of phthalazine), 129.55 (C-1 of 4-methylbenzene), 129.90 (C-10 of phthalazine), 132.30 (C-3 of 4-methylbenzene), 132.51 (C-7 of phthalazine), 134.14 (C-6 of phthalazine), 136.25 (C-1 of 4-nitrobenzene), 138.88 (C-4 of 4-methylbenzene), 143.12 (C-4 of triazole), 145.25 (C-1 of 4-nitrobenzene), 147.69 (C-4 of phthalazine), 158.30 (CO, C-1 of phthalazine); LC–MS (m/z): 453 ($M+1$, 100 %); Anal. calcd. For $C_{25}H_{20}N_6O_3$; Calcd: C, 66.36; H, 4.46; N, 18.57; found: C, 66.34; H, 4.47; N, 18.58.

*2-{[1-(2,4-dichlorobenzyl)-1H-1,2,3-triazol-4-yl]methyl}-4-(4-methylphenyl)phthalazin-1(2H)-one (**5c**)*

Yellow microcrystals; Yield: 79 %; mp: 176–178 °C; IR (KBr ν_{max}/cm^{-1}): 2968 (C–H–str), 1664 (C=O), 1206 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.42 (s, 3H, CH_3), 5.45 (s, 2H, CH_2), 5.67 (s, 2H, CH_2), 7.23 (d, 1H, ArH), 7.36 (d, 2H, ArH, J =8 Hz), 7.44 (m, 3H, ArH), 7.71 (2H, ArH), 7.91 (2H, ArH), 8.15 (s, 1H, 1,2,3-triazole H), 8.38 (1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 21.38 (CH_3), 46.45 (N–CH_2), 50.45 (N–CH_2), 124.92 (C-5 of triazole), 127.03 (C-5 of phthalazine), 127.19 (C-8 of phthalazine), 127.95 (C-5 of 2,4-dichlorobenzene), 128.34 (C-2 of methylbenzene), 129.08 (C-9 of phthalazine), 129.58 (C-1 of methylbenzene),129.77 (C-10 of phthalazine), 132.21 (C-3 of 2,4-dichlorobenzene), 132.26 (C-3 of methylbenzene), 132.44 (C-6 of 2,4-dichlorobenzene), 132.95 (C-7 of phthalazine), 134.12 (C-2 of 2,4-dichlorobenzene), 134.37 (C-6 of phthalazine), 139.20 (C-4 of 2,4-dichlorobenzene), 143.43 (C-5 of triazole), 144.22 (C-1 of 2,4-dichlorobenzene), 144.89 (C-4 of methylbenzene), 146.87 (C-4 of phthalazine), 158.33 (CO, C-1 of phthalazine); LC–MS (m/z): 477 ($M+1$, 100 %); Anal. calcd. For $C_{25}H_{19}Cl_2N_5O$; Calcd: C, 63.03; H, 4.02; N, 14.70; found: C, 63.03; H, 4.01; N, 14.72.

*2-[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]-4-(4-methylphenyl)phthalazin-1(2H)-one (**5d**)*

White microcrystals; Yield: 85 %; mp: 174–176 °C; IR (KBr ν_{max}/cm^{-1}): 2963 (C–H–str), 1662 (C=O), 1206 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.42 (s, 3H, CH_3), 5.44 (s, 2H, CH_2), 5.56 (s, 2H, CH_2), 7.29–7.37 (m, 7H, ArH), 7.45 (d, 2H, ArH), 7.72 (1H, ArH), 7.91 (d, 2H, ArH), 8.16 (s, 1H, 1,2,3-triazole H), 8.38 (m, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 21.38 (CH_3), 46.65 (N–CH_2), 53.23 (N–CH_2), 124.41 (C-5 of triazole), 127.02 (C-5 of phthalazine), 127.20 (C-8 of phthalazine), 127.96 (C-2 of methylbenzene), 128.42 (C-9 of phthalazine), 128.58 (C-1 of methylbenzene), 129.12 (C-3 of phenyl ring), 129.19 (C-10 of phthalazine), 129.58 (C-2 of phenyl ring), 129.78 (C-3 of chlorobenzene), 132.21 (C-7 of phthalazine), 132.43 (C-1 of phenyl ring), 134.11 (C-6 of phthalazine), 136.53 (C-4 of methylbenzene),139.19 (C-4 of phenyl ring), 143.53 (C-4 of triazole), 146.87 (C-4 of phthalazine), 158.32 (CO, C-1 of phthalazine); LC–MS (m/z): 408 ($M+1$, 100 %); Anal. calcd. For $C_{25}H_{21}N_5O$; Calcd: C, 73.69; H, 5.19; N, 17.19; found: C, 73.71; H, 5.18; N, 17.17.

*2-{[1-(3-methylbenzyl)-1H-1,2,3-triazol-4-yl]methyl}-4-(4-chlorophenyl) phthalazin-1(2H)-one (**5e**)*

White microcrystals; Yield: 72 %; mp: 210–212 °C; IR (KBr ν_{max}/cm^{-1}): 2978 (C–H–str), 1704 (C=O), 1222 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.32 (s, 3H, CH_3), 5.41 (s, 2H, CH_2), 5.51 (s, 2H, CH_2), 7.11 (m, 3H, ArH), 7.25 (s, 1H, ArH), 7.61–7.69 (m, 4H, ArH), 7.74 (m, 1H, ArH), 7.90–7.92 (m, 2H, ArH), 8.29 (s, 1H, 1,2,3-triazole H), 8.38 (1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 20.91 (CH_3), 46.22 (N–CH_2), 52.75 (N–CH_2), 124.01 (C-5 of triazole), 125.06 (C-5 of phthalazine), 126.56 (C-8 of phthalazine), 127.07 (C-4 of 3-methylbenzene), 127.15 (C-6 of 3-methylbenzene), 128.05 (C-2 of 3-methylbenzene), 128.65 (C-9 of phthalazine), 128.78 (C-3 of chlorobenzene), 128.99 (C-5 of 3-methylbenzene), 129.18 (C-1 of chlorobenzene), 131.77 (C-10 of phthalazine), 132.59 (C-2 of chlorobenzene), 133.95 (C-7 of phthalazine), 134.25 (C-6 of

phthalazine), 134.55 (C-4 of chlorobenzene), 138.02 (C-4 of triazole), 139.05 (C-3 of 3-methylbenzene), 139.75 (C-1 of 3-methylbenzene), 149.40 (C-4 of phthalazine), 157.98 (CO); LC–MS (m/z): 443 ($M+1$, 100 %); Anal. calcd. For $C_{25}H_{20}ClN_5O$; Calcd: C, 67.95; H, 4.56; N, 15.85; found: C, 67.97; H, 5.51; N, 15.87.

*2-{[1-(4-Nitrobenzyl)-1H-1,2,3-triazol-4-yl]methyl}-4-(4-chlorophenyl)phthalazin-1(2H)-one (**5f**)*

Yellow microcrystals; Yield: 75 %; mp: 180–182 °C; IR (KBr ν_{max}/cm^{-1}): 2965 (C–H–str), 1660 (C=O), 1208 (N=N), 801 (C–H bond); ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.52 (s, 2H, CH_2), 5.80 (s, 2H, CH_2), 7.57 (d, 2H, ArH), 7.67 (m, 4H, ArH), 7.76 (m, 1H, ArH), 7.98 (m, 2H, ArH), 8.27 (d, 2H, ArH), 8.31 (s, 1H, 1,2,3-triazole H), 8.44 (m, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 46.73 (N–CH_2), 52.33 (N–CH_2), 124.35 (C-3 of 4-nitrobenzene), 124.92 (C-5 of triazole), 127.02 (C-5 of phthalazine), 127.07 (C-8 of phthalazine), 127.92 (C-2 of 4-nitrobenzene), 128.86 (C-3 of 4-chlorobenzene), 129.13 (C-9 of phthalazine), 129.51 (C-10 of phthalazine), 131.75, 132.61 (C-7 of phthalazine), 133.88 (C-6 of phthalazine), 134.26 (C-3 of 4-chlorobenzene) 4, 134.54 (C-1 of 4-nitrobenzene), 143.60 (C-1 of 4-nitrobenzene), 143.91(C-4 of triazole), 145.80 (C-1 of 4-nitrobenzene), 147.67(C-4 of phthalazine), 158.34 (CO, C-1 of phthalazine); LC–MS (m/z): 474 ($M+1$, 100 %); Anal. calcd. For $C_{24}H_{17}ClN_6O_3$; Calcd: C, 60.96; H, 3.62; N, 17.77; found: C, 60.99; H, 3.60; N, 17.76.

*2-{[1-(2,4-Dichlorobenzyl)-1H-1,2,3-triazol-4-yl]methyl}-4-(4-chlorophenyl)phthalazin-1(2H)-one (**5g**)*

Off-white microcrystals; Yield: 76 %; mp: 188–190 °C; IR (KBr ν_{max}/cm^{-1}): 2963 (C–H–str), 1662 (C=O), 1206 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.52 (s, 2H, CH_2), 5.81 (s, 2H, CH_2), 7.57 (m, 3H, ArH), 7.69–7.78 (m, 5H, ArH), 7.95 (m, 2H, ArH), 8.12 (s, 1H, 1,2,3-triazole H), 8.44 (m, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 46.70 (N–CH_2), 52.35 (N–CH_2), 124.96 (C-5 of triazole), 126.98 (C-5 of phthalazine), 127.07 (C-8 of phthalazine), 127.95(C-5 of 2,4-dichlorobenzene), 128.92 (C-9 of phthalazine), 129.15 (C-3 of 4-chlorobenzene), 129.76 (C-1 of 4-chlorobenzene), 130.25 (C-10 of phthalazine), 130.55 (C-2 of 4-chlorobenzene), 130.79 (C-3 of 2,4-dichlorobenzene), 130.98 (C-6 of 2,4-dichlorobenzene), 132.76 (C-7 of phthalazine), 134.40 (C-2 of 2,4-dichlorobenzene), 134.55 (C-6 of phthalazine), 135.00 (C-6 of 2,4-dichlorobenzene), 141.20 (C-4 of 2,4-dichlorobenzene), 142.70 (C-4 of triazole), 147.98 (C-4 of phthalazine), 158.32 (CO, C-1 of phthalazine); LC–MS (m/z): 497 ($M+1$, 100 %); Anal. calcd. For $C_{24}H_{16}Cl_3N_5O$; Calcd: C, 58.03; H, 3.25; N, 14.10; found: C, 58.05; H, 3.24; N, 14.09.

*2-[(1-Benzyl-1H-1,2,3-triazol-4-yl)methyl]-4-(4-chlorophenyl)phthalazin-1(2H)-one (**5h**)*

White microcrystals; Yield: 89 %; mp: 194–196 °C; IR (KBr ν_{max}/cm^{-1}): 2963 (C–H–str), 1662 (C=O), 1206 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.52 (s, 2H, CH_2), 5.81 (s, 2H, CH_2), 7.57 (2H, ArH), 7.69–7.78 (m, 6H, ArH), 7.95 (2H, ArH), 8.27–8.31 (m, 2H, ArH and 1,2,3-triazole H), 8.44 (m, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 46.76 (N–CH_2), 52.35 (N–CH_2), 123.98 (C-5 of triazole), 126.99 (C-5 of phthalazine), 127.08 (C-8 of phthalazine), 127.97 (C-9 of phthalazine), 128.39 (C-3 of chlorobenzene), 128.55 (C-3 of phenyl ring), 128.75 (C-1 of chlorobenzene), 129.15 (C-10 of phthalazine), 129.99 (C-2 of phenyl ring), 131.78 (C-7 of phthalazine), 132.55 (C-1 of phenyl ring), 133.94 (C-6 of phthalazine), 134.22 (C-4 of chlorobenzene), 142.50 (C-5 of triazole), 145.70 (C-4 of phthalazine), 158.32 (CO, C-1 of phthalazine); LC–MS (m/z): 429 ($M+1$, 100 %); Anal. calcd. For $C_{24}H_{18}ClN_5O$; Calcd: C, 67.37; H, 4.24; N, 16.37; found: C, 67.39; H, 4.23; N, 16.35.

*2-{[1-(4-hydroxybenzoyl)-1H-1,2,3-triazol-4-yl]methyl}-4-(4-methylphenyl)phthalazin-1(2H)-one (**6a**)*

Off-white microcrystals; Yield: 56 %; mp: 220 °C (decomposes); IR (KBr ν_{max}/cm^{-1}): 3273 (O–H str), 2961 (C–H–str), 1684 (C=O), 1648 (C=O), 1206 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.1 (s, 3H, CH_3), 5.52 (s, 2H, N–CH_2), 5.81 (s, 2H, $COCH_2$), 6.89 (m, 2H, ArH), 7.32 (d, 2H, ArH), 7.41 (d, 2H, ArH), 7.69 (m, 1H, ArH), 7.71–7.76 (m, 4H, ArH), 8.1 (s, 1H, 1,2,3-triazole H), 8.46 (m,1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 21.40 (CH_3), 46.83 (N–CH_2), 54.18 (N–CH_2), 115.05 (C-3 of 4-hydroxybenzene), 126.28 (C-5 of triazole), 127.04 (C-5 of phthalazine), 127.28 (C-8 of phthalazine), 127.97 (C-2 of methylbenzene), 128.11 (C-9 of phthalazine), 128.50 (C-1 of methylbenzene), 129.15 (C-10 of phthalazine), 129.63 (C-2 of 4-hydroxybenzene), 129.85 (C-3 of methylbenzene), 132.16 (C-7 of phthalazine), 132.48 (C-1 of 4-hydroxybenzene), 134.16 (C-6 of phthalazine), 137.24 (C-4 of triazole), 142.45 (C-4 of methylbenzene), 146.98 (C-4 of phthalazine), 156.05 (C-4,C-OH) 158.42 (CO, C-1 of phthalazine), 188.92 (CO); LC–MS (m/z): 452 ($M+1$, 100 %); Anal. calcd. For $C_{26}H_{21}N_5O_3$; Calcd: C, 69.17; H, 4.69; N, 15.51; found: C, 69.19; H, 4.70; N, 15.49.

*2-{[1-(2,4-dichlorobenzoyl)-1H-1,2,3-triazol-4-yl]methyl}-4-(4-methylphenyl)phthalazin-1(2H)-one (**6b**)*

Yellow microcrystals; Yield: 61 %; mp: 213 °C (decomposes); IR (KBr ν_{max}/cm^{-1}): 2976 (C–H–str), 1705 (C=O), 1652 (C=O), 1220 (N=N); ^{1}H NMR (400 MHz, DMSO-

d_6): δ 2.51 (s, 3H, CH_3), 5.49 (s, 2H, NCH_2), 6.02 (s, 2H, $COCH_2$), 7.38 (d, 2H, ArH, $J = 7.6$ Hz), 7.51 (d, 2H, ArH, $J = 7.6$ Hz), 7.64 (dd, 1H, ArH), 7.75 (m, 1H, ArH), 7.82 (d,1H, ArH), 7.93–7.99 (m, 3H, ArH), 8.11 (s, 1H, 1,2,3-triazole H), 8.40 (d,1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 21.47 (CH_3), 46.40 (N–CH_2), 50.42 (N–CH_2), 124.93 (C-5 of triazole), 127.05 (C-5 of phthalazine), 127.21 (C-8 of phthalazine), 127.95 (C-5 of 2,4-dichlorobenzene), 128.10 (C-2 of methylbenzene), 128.34 (C-9 of phthalazine), 128.82 (C-1 of methylbenzene), 129.15 (C-10 of phthalazine), 129.62 (C-6 of 2,4-dichlorobenzene), 129.78 (C-3 of methylbenzene), 132.30 (C-3 of 2,4-dichlorobenzene), 132.51 (C-7 of phthalazine), 133.00 (C-2 of 2,4-dichlorobenzene), 134.08 (C-6 of phthalazine), 134.40 (C-1 of 2,4-dichlorobenzene), 137.20 (C-4 of triazole), 139.25 (C-4 of 2,4-dichlorobenzene), 142.45 (C-2 of methylbenzene), 147.00 (C-4 of phthalazine), 158.50 (CO, C-1 of phthalazine), 189.09 (CO); LC–MS (m/z): 505 (M + 1, 100 %); Anal. calcd. For $C_{26}H_{19}Cl_2N_5O_2$; Calcd: C, 61.91; H, 3.80; N, 14.06; found: C, 61.90; H, 3.81; N, 14.06.

*2-{[1-(4-methylbenzoyl)-1H-1,2,3-triazol-4-yl]methyl}-4-(4-methylphenyl)phthalazin-1(2H)-one (**6c**)*

Yellow microcrystals; Yield: 58 %; mp: 200 °C (decomposes); IR (KBr ν_{max}/cm^{-1}): 2963 (C–H–str), 1682 (C=O), 1642 (C=O), 1206 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.40 (s, 6H, CH_3), 5.48 (s, 2H, NCH_2), 6.09 (s, 2H, $COCH_2$), 7.37 (4H, ArH), 7.50 (d, 2H, ArH), 7.72 (m, 1H, ArH), 7.91 (m, 3H, ArH), 8.06 (s, 1H, 1,2,3-triazole H), 8.38 (m, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 21.39 (CH_3), 21.73 (CH_3), 46.81 (N–CH_2), 56.15 (N–CH_2), 126.00 (C-5 of triazole), 127.03 (C-5 of phthalazine), 127.23 (C-8 of phthalazine), 127.99 (C-2 of methylbenzene), 128.70 (C-9 of phthalazine), 129.13 (C-1 of methylbenzene), 129.61 (C-2 of methylbenzene), 129.85 (C-10 of phthalazine), 129.96 (C-3 of methylbenzene), 132.12 (C-3 of methylbenzene), 132.23 (C-7 of phthalazine), 132.46 (C'-1 of methylbenzene), 134.14 (C-6 of phthalazine), 139.21 (C-4 of triazole), 143.12 (C-4 of methylbenzene), 145.25 (C-3 of methylbenzene), 146.89 (C-4 of phthalazine), 158.32 (CO, C-1 of phthalazine), 188.90 (CO); LC–MS (m/z): 450 (M + 1, 100 %); Anal. calcd. For $C_{27}H_{23}N_5O_2$; Calcd: C, 72.14; H, 5.16; N, 15.58; found: C, 72.12; H, 5.14; N, 15.61.

*2-{[1-(4-hydroxybenzoyl)-1H-1,2,3-triazol-4-yl]methyl}-4-(4-chlorophenyl)phthalazin-1(2H)-one (**6d**)*

Yellow microcrystals; Yield: 52 %; mp: 216 °C (decomposes); IR (KBr ν_{max}/cm^{-1}): 3390 (O–H str), 2979 (C–H–str), 1680 (C=O), 1644 (C=O), 1208 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.50 (s, 2H, NCH_2), 6.02 (s, 2H, $COCH_2$), 6.91 (d, 2H, ArH, $J = 8$Hz), 7.63–7.68 (m, 4H, ArH), 7.73 (m, 1H, ArH), 7.93 (m, 4H, ArH), 8.07 (s, 1H, 1,2,3-triazole H), 8.41 (m, 1H, ArH), 10.59 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): 46.70 (N–CH_2), 52.38 (N–CH_2), 115.03 (C-3 of 4-hydroxybenzene), 125.02 (C-5 of triazole), 127.01 (C-5 of phthalazine), 127.11 (C-8 of phthalazine), 127.99 (C-9 of phthalazine), 128.50 (C-3 of chlorobenzene), 128.95 (C-1 of chlorobenzene), 129.16 (C-10 of phthalazine), 129.30 (C-2 of 4-hydroxybenzene), 131.77 (C-2 of chlorobenzene), 132.02 (C-7 of phthalazine), 132.61 (C-1 of 4-hydroxybenzene), 133.95 (C-6 of phthalazine), 134.23 (C-4 of chlorobenzene), 134.50 (C-4 of triazole), 145.79 (C-4 of phthalazine), 156.09 (C-4,C-OH), 158.20 (CO, C-1 of phthalazine), 189.15 (CO); LC–MS (m/z): 473 (M + 1, 100 %); Anal. calcd. For $C_{25}H_{18}ClN_5O_3$; Calcd: C, 63.63; H, 3.84; N, 14.84; found: C, 63.64; H, 3.85; N, 14.82.

*2-{[1-(2,4-dichlorobenzoyl)-1H-1,2,3-triazol-4-yl]methyl}-4-(4-chlorophenyl) phthalazin-1(2H)-one (**6e**)*

Pale yellow microcrystals; Yield: 49 %; mp: 225 °C (decomposes); IR (KBr ν_{max}/cm^{-1}): 2980 (C–H–str), 1700 (C=O), 1648 (C=O), 1225 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.53 (s, 2H, NCH_2), 6.05 (s, 2H, $COCH_2$), 7.09 (d, 2H, ArH), 7.67 (d, 2H, ArH), 7.71–7.91 (m, 6H, ArH), 8.11 (s, 1H, 1,2,3-triazole H), 8.37 (d, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 46.72 (N–CH_2), 52.40 (N–CH_2), 124.99 (C-5 of triazole), 127.01 (C-5 of phthalazine), 127.10 (C-8 of phthalazine), 127.89 (C-5 of 2,4-dichlorobenzene),128.09 (C-9 of phthalazine), 128.90 (C-3 of chlorobenzene), 129.05 (C-1 of chlorobenzene), 129.20 (C-10 of phthalazine),129.62 (C-2 of chlorobenzene), 130.78 (C-6 of 2,4-dichlorobenzene), 131.50 (C-3 of 2,4-dichlorobenzene), 132.25 (C-7 of phthalazine), 133.35 (C-2 of 2,4-dichlorobenzene), 133.71 (C-6 of phthalazine), 134.33 (C-4 of chlorobenzene), 134.80 (C-1 of 2,4-dichlorobenzene), 134.98 (C-4 of triazole), 139.98 (C-4 of 2,4-dichlorobenzene), 146.90 (C-4 of phthalazine), 159.20 (CO, C-1 of phthalazine), 192.15 (CO); LC–MS (m/z): 525 (M + 1, 100 %); Anal. calcd. For $C_{25}H_{16}Cl_3N_5O_2$; Calcd: C, 57.22; H, 3.07; N, 13.35; found: C, 57.25; H, 3.09; N, 13.30.

*2-{[1-(4-methylbenzoyl)-1H-1,2,3-triazol-4-yl]methyl}-4-(4-chlorophenyl) phthalazin-1(2H)-one (**6f**)*

White microcrystals; Yield: 62 %; mp: 192 °C (decomposes); IR (KBr ν_{max}/cm^{-1}): 2963 (C–H–str), 1688 (C=O), 1638 (C=O), 1206 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.50 (s, 3H, CH_3), 5.52 (s, 2H, NCH_2), 5.81 (s, 2H, $COCH_2$), 7.37 (d, 2H, ArH), 7.42 (d, 2H, ArH), 7.69–7.81

(m, 5H, ArH), 7.95 (d, 2H, ArH), 8.09 (s, 1H, 1,2,3-triazole H), 8.43 (d, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 21.73 (CH_3), 46.88 (N–CH_2), 54.19 (N–CH_2), 124.99 (C-5 of triazole), 126.05 (C-5 of phthalazine), 126.99 (C-8 of phthalazine), 127.99 (C-9 of phthalazine), 128.56 (C-3 of chlorobenzene), 128.70 (C-1 of chlorobenzene), 128.92 (C-10 of phthalazine), 129.15 (C-2 of methylbenzene), 129.49 (C-2 of chlorobenzene), 130 (C-3 of methylbenzene), 131.80 (C-7 of phthalazine), 132.15 (C-1 of methylbenzene), 133.94 (C-6 of phthalazine), 134.22 (C-4 of chlorobenzene), 134.53 (C-4 of triazole), 142.98 (C-4 of methylbenzene), 145.73 (C-4 of phthalazine), 158.32 (CO, C-1 of phthalazine), 192.10 (CO); LC–MS (m/z): 471(M + 1, 100 %); Anal. calcd. For $C_{26}H_{20}ClN_5O2$; Calcd: C, 66.45; H, 4.29; N, 14.90; found: C, 66.43; H, 4.31; N, 14.91.

*2-{[1-isopropyl-1H-1,2,3-triazol-4-yl]methyl}-4-(4-methylphenyl)phthalazin-1(2H)-one (**7a**)*

White microcrystals; Yield: 76 %; mp: 150–152 °C; IR (KBr ν_{max}/cm^{-1}): 2975 (C–H–str), 1672 (C=O), 1206 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.49 (d, 6H, CH_3), 4.80 (m, 1H, CH), 5.48 (s, 2H, NCH_2), 7.40 (d, 2H, ArH, J = 8 Hz), 7.49 (d, 2H, ArH, J = 8 Hz), 7.75–7.96 (m, 3H, ArH), 8.11 (s, 1H, 1,2,3-triazole H), 8.38 (d, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 21.40 (CH_3), 23.15 (isopropyl CH_3), 46.89 (N–CH), 52.15 (N–CH_2), 123.11 (C-4 of triazole), 127.00 (C-8 of phthalazine), 127.20 (C-1 of methylbenzene), 127.97 (C-2 of methylbenzene), 129.12 (C-3 of methylbenzene), 129.59 (C-5 of phthalazine), 129.80 (C-10 of phthalazine), 132.21 (C-7 of phthalazine), 132.44 (C-6 of phthalazine), 134.12 (C-9 of phthalazine), 139.20 (C-4 of methylbenzene), 143.10 (C-5 of triazole), 146.90 (C-4 of phthalazine), 158.30 (CO, C-1 of phthalazine); LC–MS (m/z): (M + 1, 100 %); Anal. calcd. For $C_{21}H_{21}N_5O$; Calcd: C, 70.17; H, 5.89; N, 19.48; found: C, 70.15; H, 5.87; N, 19.51.

*2-{[1-(2-propenyl)-1H-1,2,3-triazol-4-yl]methyl}-4-(4-methylphenyl)phthalazin-1(2H)-one (**7b**)*

Off-white microcrystals; Yield: 62 %; mp: 108–110 °C; IR (KBr ν_{max}/cm^{-1}): 2979 (C–H–str), 1698 (C=O), 1221 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.42 (s, 3H, CH_3), 4.98 (d, 2H, CH_2), 5.15–5.25 (dd, 2H, allylic CH_2), 5.45 (s, 2H, NCH_2), 5.98–6.08 (m, 1H, allylic CH), 7.38 (d, 2H, ArH, J = 8Hz), 7.47 (d, 2H, ArH, J = 8 Hz), 7.73 (m, 1H, ArH), 7.92 (m, 2H, ArH), 8.05 (s, 1H, 1,2,3-triazole H), 8.39 (1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 21.38 (CH_3), 46.82 (N–CH_2), 52.11 (N–CH_2), 119.24 (CH_2), 124.20 (C-4 of triazole), 127.02 (C-8 of phthalazine), 127.21 (C-1 of methylbenzene), 127.99 (C-2 of methylbenzene), 129.14 (C-3 of methylbenzene), 129.60 (C-5 of phthalazine), 129.82 (C-10 of phthalazine), 132.23 (C-7 of phthalazine), 132.43 (C-6 of phthalazine), 133.28 (CH of propelene), 134.12 (C-9 of phthalazine), 139.20 (C-4 of methylbenzene), 143.36 (C-5 of triazole), 146.87 (C-4 of phthalazine), 158.33 (CO, C-1 of phthalazine); LC–MS (m/z): (M + 1, 100 %); Anal. calcd. For $C_{21}H_{19}N_5O$; Calcd: C, 70.57; H, 5.36; N, 19.59; found: C, 70.55; H, 5.35; N, 19.61.

*2-[(1-Isopropyl-1H-1,2,3-triazol-4-ylm)ethyl]-4-(4-chlorophenyl)phthalazin-1(2H)-one (**7c**)*

White microcrystals; Yield: 78 %; mp: 162–164 °C; IR (KBr ν_{max}/cm^{-1}): 2965(C–H–str), 1708 (C=O), 1225 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.45 (d, 6H, CH_3), 4.78 (m, 1H, CH), 5.44 (s, 2H, NCH_2), 7.64 (m, 4H, ArH), 7.72 (m, 1H, ArH), 7.93 (m, 2H, ArH), 8.13 (s, 1H, 1,2,3-triazole H), 8.39 (1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 23.15 (CH_3), 46.96 (N–CH), 52.77 (N–CH_2), 121.97 (C-4 of triazole), 126.99 (C-8 of phthalazine), 127.09 (C-3 of chlorobenzene), 127.98 (C-1 of chlorobenzene), 128.91 (C-5 of phthalazine), 129.15 (C-10 of phthalazine), 131.79 (C-2 of chlorobenzene), 132.57 (C-7 of phthalazine), 133.94 (C-6 of phthalazine), 134.22 (C-9 of phthalazine), 134.53 (C-4 of chlorobenzene), 142.98 (C-5 of triazole), 145.73 (C-4 of phthalazine), 158.33 (CO, C-1 of phthalazine); LC–MS (m/z): 381 (M + 1, 100 %); Anal. calcd. For $C_{20}H_{18}ClN_5O$; Calcd: C, 63.24; H, 4.78; N, 18.44; found: C, 63.23; H, 4.76; N, 18.46.

*2-{[1-(2-Propenyl)-1H-1,2,3-triazol-4-yl]methyl}-4-(4-chlorophenyl)phthalazin-1(2H)-one (**7d**)*

Cream coloured microcrystals; Yield: 69 %; mp: 120–122 °C; IR (KBr ν_{max}/cm^{-1}): 2979 (C–H–str), 1698 (C=O), 1221 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.92 (d, 2H, CH_2), 5.11–5.23 (dd, 2H, allylic CH_2), 5.43 (s, 2H, NCH_2), 5.96–6.07 (m, 1H, allylic CH), 7.63 (d, 2H, ArH, J = 8Hz), 7.71 (d, 2H, ArH, J = 8 Hz), 7.78 (d, 1H, ArH), 7.92 (m, 2H, ArH), 8.11 (s, 1H, 1,2,3-triazole H), 8.41 (d, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 46.88 (N–CH_2), 52.17 (N–CH_2), 119.21 (CH_2), 122.95 (C-4 of triazole), 126.98 (C-8 of phthalazine), 127.08 (C-3 of chlorobenzene), 127.92 (C-1 of chlorobenzene), 126.88 (C-5 of phthalazine), 129.13 (C-3 of chlorobenzene), 131.77 (C-2 of chlorobenzene), 132.55 (C-7 of phthalazine), 133.44 (CH of propelene), 133.92 (C-6 of phthalazine), 134.20 (C-9 of phthalazine), 134.51 (C-4 of chlorobenzene), 142.95 (C-5 of triazole), 145.70 (C-4 of phthalazine), 158.28 (CO, C-1 of phthalazine); LC–MS (m/z): 379 (M+1, 100 %); Anal. calcd. For $C_{20}H_{16}ClN_5O$; Calcd: C, 63.58; H, 4.27; N, 18.54; found: C, 63.55; H, 4.25; N, 18.57.

Results and discussion

Chemistry

Phthalazine derivatives were synthesized from 2-(4-methyl/chloro benzyloxy) benzoic acid by esterification followed by hydrazinolysis. The 4-(4-methyl/chlorophenyl) phthalazine-1-ol is then condensed with propargyl bromide to get 4-(4-chloro/methylphenyl)-2-prop-2-yn-1-ylphthalazin-1(2H)-one (**4a**, **b**). The targeted regioselective 1,4-disubstituted 1,2,3-triazole derivatives (**5a–h**, **6a–f** and **7a–d**) were synthesized by multicomponent one pot click chemistry approach, by reacting 4-(4-chloro/methylphenyl)-2-prop-2-yn-1-ylphthalazin-1(2H)-one (**4a**, **b**) with various benzyl/phenacyl/alkyl bromides. Newly synthesized compounds were characterized by IR, NMR, mass spectral and C, H, N elemental analyses.

In the IR spectrum of **4a**, the carbonyl absorption band was observed at 1657/cm^{-1}. The acetylenic absorption band was seen at 2215/cm^{-1}. Further in the ^{1}H NMR spectrum of 4-(4-methylphenyl)-2-prop-2-yn-1-ylphthalazin-1(2H)-one **4a**, the methyl group attached to the phenyl ring came into resonance as a singlet at δ 2.40 integrating for three protons. The acetylenic proton gave a distinct peak at δ 3.32. The –NCH$_2$ protons appeared as a singlet at δ 4.97. The signals due to aromatic protons of phenyl ring appeared as two doublets centred at 7.37 and 7.48 integrating for two protons each. The peak due to aromatic protons of phthalazine ring appeared at 7.71, 7.91 and 8.36 corresponding to four protons.

In the IR spectrum of **5a**, the acetylinic triple bond stretching at 2215/cm^{-1} gets disappeared. In the ^{1}H NMR spectrum the methyl groups attached to the phenyl ring came into resonance as singlet at δ 2.24 and 2.40, respectively, integrating for three protons each. The CH$_2$ protons attached to phthalazine nitrogen came into resonance at δ 5.41 while the CH$_2$ proton attached to the triazole appeared at δ 5.49 each integrating for two protons. The signals due to aromatic protons appeared as a multiplet at δ 7.09 corresponding to three protons, δ 7.22 corresponds to one proton, doublets at δ 7.34 and δ 7.44 corresponds to two protons each, a multiplet centred at δ 7.7 corresponds to one proton, a multiplet centred at δ 7.9 corresponds to two protons and a multiplet centred at δ 8.37 corresponds to one proton. The lone triazole proton appeared as a singlet at δ 8.35. Further the mass spectrum of this compound showed the molecular ion peak at m/z 422 (*M* + 1 peak, 100 %) consistent with the molecular formula $C_{26}H_{23}N_5O$. The characterization data of the newly synthesized compounds are given in the experimental section.

Pharmacology

The antibacterial screening revealed that, all the tested compounds showed good inhibition against various microbial strains compared to the standard drug. Among them, compounds **5c**, **5g**, **5h**, **6b** and **6e** showed excellent antibacterial activity. The data further reveals that 2,4-dichlorophenyl substituted compounds are showing enhanced antibacterial activity. Similarly compound **5h** with a phenyl substitution is also showing very good antibacterial activity comparable with the standard drug Streptomycin. All other compounds are showing moderate activity against all the tested bacterial strains compared to the standard drug.

The results of in vitro antifungal activities of new derivatives **5a–h, 6a–f** and **7a–d** indicate that, among the tested compounds **5g** and **6d** are active against all tested fungal strains. Compound **5g** bearing 2,4-dichlorophenyl substituent in 1,2,3-triazole ring and 4-chlorophenyl substituent in phthalazine moiety and compound **6d** possessing 4-hydroxyphenyl substituent in 1,2,3-triazole ring, and 4-chlorophenyl substituent in phthalazine are the leads among the tested compounds. All other compounds are showing moderate to feeble activity against all the tested fungal strains compared to the standard drug fluconazole.

The free radical-scavenging activity of the final compounds was measured by DPPH. Antioxidant activity result shows that 1,2,3-triazole derivatives **5a, 5f** and **7c** showed significant antioxidant property when compared with the standard butylhydroxytoluene (BHT). Compounds **5a, 5f** and **7c** contains 3-methyl phenyl, 4-nitrophenyl and isopropyl substituents, respectively, in 1,2,3-triazole ring, which may be accounted for the enhanced activity.

Biological activity

Antimicrobial studies: antibacterial studies

The newly synthesized compounds (**5a–h, 6a–f** and **7a–d**) were screened for their in vitro antibacterial activity against *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853) and *Bacillus subtilis* (MTCC- 441) by well-plate method (zone of inhibition) in Muller Hinton agar (Leandro et al., 1995; Beth et al., 2000). The test compounds were dissolved in DMSO at concentrations of 0.5 and 1.0 mg/mL.

All bacterial strains were maintained on nutrient agar medium at 37 °C. The cultures were inoculated in fresh 10 mL Nutrient Broth to yield an initial suspension of approximately 10–100 CFU/mL. All broths were then incubated statically at 37 °C for 18–24 h. The bacterial suspensions were diluted 10 fold in distilled water and 0.1 mL of the bacterial suspension was spread on nutrient agar in order to give a population of approximately 10^6 CFU/plate. The wells were dug in each petri plate by sterilized cork borer. The compounds were dissolved in DMSO and appropriate dilutions were made (1 and 0.5 mg/mL). Each

Table 1 Antibacterial activity of title compounds **5a–h**, **6a–f** and **7a–d**

Compound no.	*Escherichia coli*		*Pseudomonas aeruginosa*		*Bacillus subtilis*	
Concentration in mg/mL	1	0.5	1	0.5	1	0.5
Control	00		00		00	
Standard Streptomycin	21.3 ± 0.17	18.4 ± 0.43	19.6 ±0 .26	17.2 ± 0.58	20.3 ± 0.14	18.2 ± 0.44
5a	12.2 ± 0.27	9.6 ± 0.21	14.3 ± 0.36	10.1 ± 0.71	11.8 ± 0.31	9.3 ± 0.29
5b	13.4 ± 0.45	10.1 ± 0.18	11.1 ± 0.62	7.6 ± 0.44	13.6 ± 0.32	10.2 ± 0.51
5c	16.3 ± 0.27	13.1 ± 0.16	14.6 ± 0.67	12.2 ± 0.30	15.4 ± 0.38	12.5 ± 0.25
5d	14.5 ± 0.52	12.3 ± 0.43	11.5 ± 0.27	9.8 ± 0.15	10.1 ± 0.40	8.8 ± 0.68
5e	14.7 ± 0.39	12.3 ± 0.28	10.3 ± 0.54	5.3 ± 0.63	14.3 ± 0.27	10.6 ± 0.31
5f	12.4 ± 0.83	07.8 ± 0.92	12.1 ± 0.27	9.8 ± 0.57	12.3 ± 0.31	10.9 ± 0.54
5g	19.4 ± 0.22	17.8 ± 0.17	16.3 ± 0.25	14.2 ± 0.79	18.5 ± 0.25	13.2 ± 0.18
5h	17.8 ± 0.21	14.5 ± 0.27	15.5 ± 0.38	12.4 ± 0.74	17.3 ± 0.64	13.6 ± 0.71
6a	10.4 ± 0.35	06.3 ± 0.31	08.7 ± 0.12	6.2 ± 0.28	05.2 ± 0.14	03.7 ± 0.57
6b	15.8 ± 0.92	12.7 ± 0.15	13.6 ± 0.53	11.5 ± 0.18	12.1 ± 0.41	10.4 ± 0.83
6c	10.5 ± 0.57	06.6 ± 0.23	12.6 ± 0.38	8.3 ± 0.24	10.5 ± 0.17	10.8 ± 0.49
6d	12.5 ± 0.36	08.2 ± 0.17	07.5 ± 0.27	4.2 ± 0.44	9.2 ± 0.62	5.7 ± 0.23
6e	17.9 ± 0.33	15.2 ± 0.29	13.6 ± 0.65	10.9 ± 0.17	12.8 ± 0.27	10.2 ± 0.44
6f	12.8 ± 0.34	10.9 ± 0.54	09.3 ± 0.25	6.2 ± 0.78	04.9 ± 0.24	03.7 ± 0.54
7a	8.6 ± 0.52	5.3 ± 0.26	8.4 ± 0.44	4.7 ± 0.32	6.2 ± 0.65	3.6 ± 0.38
7b	00	00	00	00	00	00
7c	10.6 ± 0.38	8.3 ± 0.24	7.5 ± 0.17	5.8 ± 0.49	00	00
7d	00	00	00	00	00	00

experiment was carried out in triplicate. After the inoculation of the organism and compound, the petri plates were incubated for 18 h at 37 °C. The diameter of zone of inhibition was measured. Streptomycin was taken as the standard drug for antibacterial screening. The result of antimicrobial activity determined for **5a–h**, **6a–f** and **7a–d** are summerised in Table 1.

Antifungal studies

The newly synthesized compounds were also screened for their antifungal activity against *Aspergillus flavus* (MTCC 3306), *Chrysosporium keratinophilum* (MTCC 2827) and *Candida albicans* (MTCC 227). The compounds were dissolved in DMSO and antimicrobial activity was determined by well-plate method (MacLowry et al., 1970; Portillo et al., 2001) at concentration of 1 and 0.5 mg/mL. The required amounts of each fungal strain were taken from the stock and suspended in 5 mL of distilled water with two drops of Tween 80. This suspension was uniformly spread on petri plates containing Potato dextrose agar media using sterile swabs. After applying the samples into the wells formed by using the same technique for tests on bacteria, the plates were incubated at 25 °C for 3 days. The plates were then examined for the presence of zones of inhibition and the results were recorded. Fluconazole was used as a positive control at a concentration of 1 mg/mL. The zone of inhibition was determined for **5a–h**, **6a–f** and **7a–d** and the results are summerised in Table 2.

Antioxidant studies: DPPH radical-scavenging assay

Free radical-scavenging capacities of the final compounds **5a–h**, **6a–f** and **7a–d** were determined using the stable DPPH (Brand-Williams et al., 1995) . The stock solution of test compounds (1 mg/mL) and DPPH (0.004 %) were prepared using 95 % methanol. Freshly prepared DPPH solution were taken in test tubes and organic compounds were then added (100 µg) to every test tube. The absorbance was measured after 10 min at 517 nm using a UV-visible spectrophotometer (Shimadzu UV-1800, Japan). BHT was used as a reference standard. Control sample was prepared without any test compounds or BHT. 95 % Methanol was used as blank.

$$\text{DPPH radical scavenging activity}(\%) = \text{Abs Control} - \text{Abs Sample}/\text{Abs Control} \times 100,$$

where 'Abs Control' is the absorbance of DPPH radical + methanol; 'Abs Sample' is the absorbance of DPPH radical + test sample/standard BHT.

Table 2 Antifungal activity of title compounds **5a–h**, **6a–f** and **7a–d**

Compound no.	*Aspergillus flavus*		*Chrysosporium keratinophilum*		*Candida albicans*	
Concentration in mg/mL	1	0.5	1	0.5	1	0.5
Control	00		00		00	
Standard Fluconazole	13 ± 0.2	10 ± 0.1	17 ± 0.2	15 ± 0.2	22 ± 0.2	20 ± 0.2
5a	03 ± 0.1	01 ± 0.1	03 ± 0.2	01 ± 0.1	04 ± 0.1	02 ± 0.2
5b	00	00	00	00	00	00
5c	00	00	00	00	00	00
5d	00	00	00	00	00	00
5e	07 ± 0.1	05 ± 0.2	06 ± 0.1	04 ± 0.2	04 ± 0.1	03 ± 0.2
5f	05 ± 0.2	03 ± 0.1	04 ± 0.1	03 ± 0.2	05 ± 0.2	02 ± 0.2
5g	10 ± 0.1	08 ± 0.2	13 ± 0.2	10 ± 0.2	15 ± 0.1	11 ± 0.1
5h	09 ± 0.2	07 ± 0.2	08 ± 0.1	07 ± 0.1	06 ± 0.2	04 ± 0.1
6a	04 ± 0.1	02 ± 0.2	05 ± 0.2	02 ± 0.2	05 ± 0.2	03 ± 0.1
6b	06 ± 0.2	04 ± 0.1	05 ± 0.2	04 ± 0.1	04 ± 0.2	03 ± 0.2
6c	09 ± 0.2	07 ± 0.2	08 ± 0.1	07 ± 0.1	06 ± 0.2	04 ± 0.1
6d	10 ± 0.1	07 ± 0.1	12 ± 0.2	10 ± 0.1	16 ± 0.2	13 ± 0.1
6e	00	00	00	00	00	00
6f	03 ± 0.2	01 ± 0.1	04 ± 0.1	02 ± 0.2	03 ± 0.1	02 ± 0.2
7a	7.3 ± 0.3	5.7 ± 0.3	4.5 ± 0.3	3.2 ± 0.6	7.1 ± 0.8	4.4 ± 0.5
7b	00	00	00	00	00	00
7c	00	00	00	00	00	00
7d	00	00	00	00	00	00

Results were presented in Table 3 and Fig. 1 shows the graphical representation of antioxidant activity.

Conclusion

Three series of phthalazine-based 1,2,3-triazoles derivatives (**5a–h, 6a–f** and **7a–d**) were synthesized by multi-step reactions in reasonably good yields and were characterized by spectral studies and elemental analyses. All the final derivatives were screened for their antimicrobial and anti-oxidant activitiy. From the biological screening results we can conclude that, a combination of two heterocyclic systems namely phthalazine and 1,2,3-triazoles has enhanced the biological effect and hence they are suitable for further modifications to get more effective antimicrobial/anti-oxidant compounds.

Acknowledgments The authors are grateful to the Management, SEQUENT SCIENTIFIC LTD, New Mangalore, India, for their invaluable support and allocation of resources for this work. The authors are also thankful to the Chairman, Department of Chemistry, Mangalore University. SPC thanks to MIT, Manipal for recording spectra.

Table 3 DPPH scavenging activity of title compounds **5a–h**, **6a–f** and **7a–d**

Compounds	DPPH assay in per cent
5a	74.3
5b	50.5
5c	40.4
5d	34.8
5e	37.2
5f	70.4
5g	52.3
5h	39.5
6a	60.5
6b	57.3
6c	14.3
6d	59.4
6e	32.3
6f	39.3
7a	38.3
7b	34.4
7c	65.8
7d	39.4
BHT	90.42

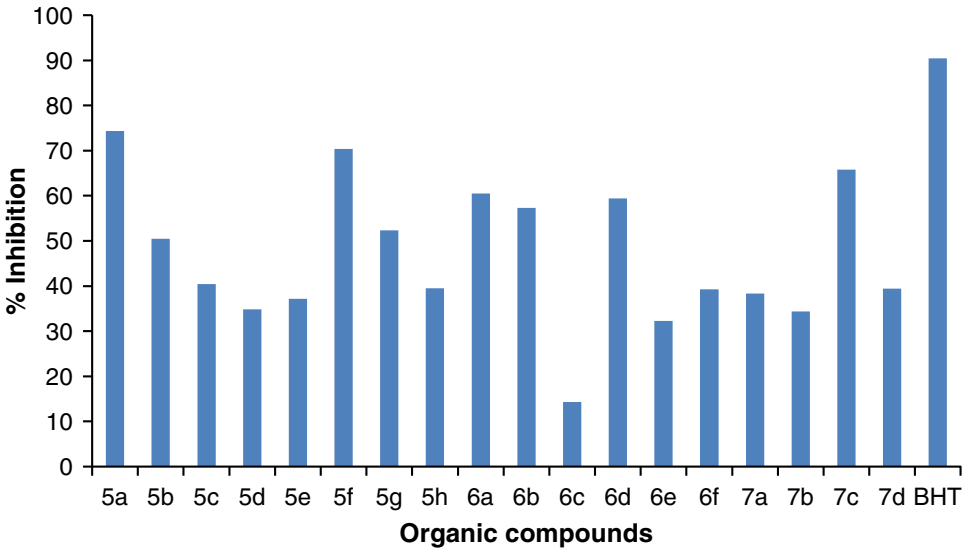


Fig. 1 DPPH scavenging activity of the compounds **5a–h**, **6a–f** and **7a–d**. "The experiment was performed in triplicate and the values expressed are as Mean ± SD"

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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