SYNTHESIS, STRUCTURAL CHARACTERIZATION OF SOME PYRAZOLO [1-5A] PYRIMIDINE AND IMIDAZO[1,2-B]-PYRAZOLE DERIVATIVES AS ANTI-CANCER ACTIVITY

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ABSTRACT
For anticancer cell line evaluation, a new sequence of pyrazolo [1-5a] pyrimidine and imidazo[1,2-b] pyrazole derivatives were synthesized. The reaction of 5-aminopyrazolo with appropriate functionalized enaminones derivatives and 2-bromoacetophenone to afford, respectively. In vitro tests were performed on the newly synthesized compounds against HepG-2 and MCF-7 cancer cells to assay their cytotoxicity. A few compounds showed promising activity as anticancer agents against MCF-7 cancer cell.

Keywords: Pyrazole, Pyrimidine, Imidazole, Enaminone, Anticancer Activity.

INTRODUCTION
Cancer is a term used to describe a group of cancerous diseases that can affect various parts of the body. The liver can develop primary cancer, in which it forms itself, or to cancer that develops elsewhere in the body and then is transferred to the liver (secondary or metastatic cancer). In addition, breast cancer is cancer that forms in the cells of the breasts. As a result, there is a constant need for new chemotherapeutic medicines for cancer care. Pyrazolo[1,5-a] pyrimidine is one of the pyrazoleopyrimidine isomers, they are purine analogue. They have a wide variety of biological activity such as anti-proliferative agents, antifungal, antimicrobial, chronic myeloid leukemia inhibitors, antioxidant, cathepsin K inhibitors, anti-tubercular, anti-inflammatory, antiviral. Currently, they reported strong cytotoxicity against several human cancer cell lines. For example, compound I showed the highest activity against HepG2, MCF7, HCT116 and HeLa cell lines with IC50 values 1.88, 0.47, 0.54 and 0.40 µg/ml, respectively. Also, Compound II was found to be the most active, with IC50 values of 1.98, 2.20, and 2.61 M, respectively, against MCF-7, BT474, and A549 cancer cell lines. Compounds III and IV were also shown to have anticancer activity against four separate cell lines (HepG2, MCF-7, A549 and Caco2). Imidazol[1,2-b] pyrazole derivatives were synthesized previously by many authors. In the last years, it was reported as an anticancer agent. For example, compounds V, VI and VII show promise as an anticancer agent with an IC50 less than 10 mM in the 6 cell lines tested.
By screening HepG-2 and MCF-7 for anticancer activity, compounds 10a-l and 12a-c derivatives carrying a phenyldiazene moiety have been prepared to produce new potent anticancer agents.

**EXPERIMENTAL**

**Synthesis of 1-phenyl-2-bromoethanone (2-bromoacetophenone) (2)**

Add anhydrous AlCl₃ (0.5 g) to a stirred solution of acetophenone (12.0 g, 0.1 mol) in dry ether (100 ml). Bromine (16.0 g, 0.2 mol) was added drop-wise over 30 min. duration with stirring for 20 min. to the resulting solution, the reaction mixture was poured on cold water. Separated the organic layer, washed twice with water, then with a solution of NaHCO₃ (10 %, 150 ml) and treated with 6 M HCl (6 ml) with NaNO₂ (0.7 g, 10 mmol) in 5 ml H₂O) was added to a solution of phenacyl bromide (10 g, 0.05 mol) in benzene (60 ml) and the reaction mixture was heated to 70 °C with intensive shaking until the aqueous layer become deep orange. The reaction mixture was cooled and the aqueous layer was removed, benzene washed and HCl acidified. Filtration, collected the solid precipitate, washed with cold water, dried and finally recrystallized from hot H₂O to produce compound 2.

**Synthesis of 3-oxo-3-phenylpropanenitrile (3)**

KCN solution (6.5 g, 0.1 mol in 30 ml H₂O) was added to a solution of phenacyl bromide (10 g, 0.05 mol) in benzene (60 ml) and the reaction mixture was heated to 70 °C with intensive shaking until the aqueous layer become deep orange. The reaction mixture was cooled and the aqueous layer was removed, benzene washed and HCl acidified. Filtration, collected the solid precipitate, washed with cold water, dried and finally recrystallized from hot H₂O to produce compound 3.

**Synthesis of 2-oxo-N,N₂-diphenylacetohydrazonoyl cyanide (6)**

In EtOH (100 ml) CH₃COONa·3H₂O (13.6 g, 0.1 mol) was introduced to a stirred solution of benzoylacetonitrile (3) (14.5 g, 0.1 mol). The mixture was chilled at 0°C after stirring for 15 min and treated with a cold solution of the required arylamine (0.1 mol) in 6 M HCl (6 ml) with NaNO₂ (0.7 g, 10 mmol) in 5 ml H₂O. The diazonium salt was added and stirred at 0-5°C for an additional 2 h, then placed in a refrigerator (4°C) for 8 h. The resulting solid was stored, washed thoroughly with H₂O and dried by filtration. To give the corresponding acetohydrazonoyl cyanide (6), the crude product was crystallized from EtOH.

**Synthesis of 3-phenyl-4-(phenyldiazene)-1H-pyrazol-5-amine derivatives (7a-c)**

Compounds (7a-c) were obtained through the reaction of acetohydrazonoyl cyanide derivatives (6a-c) with 98 % NH₂-NH₂·H₂O in n-BuOH and 4 h reflux. To afford compounds (7a-c), the product obtained was filtered, dried and crystallized by EtOH.
3-phenyl-4-(phenyldiazenyl)-1H-pyrazol-5-amine (7a)
Yield (71%), m.p. 217°C; IR (KBr, ν cm⁻¹): 3330-3195 (NH+NH₂), 1H NMR (DSMO-dš, ppm) δ 6.2 (s, 2H, D₂O-exchangeable, NH₂), 7.30-7.51 (m, 6H, 3H Ar+3H ph), 7.73 (d, J = 7.8 Hz, 2H (o, Ar)), 8.13 (d, J = 8.5 Hz, 2H (o, ph)), 12.09 (s, 1H, D₂O-exchangeable, NH); 13C NMR (DSMO-dš, ppm) 95.35, 126.30, 127.39, 127.93, 128.33, 128.34, 128.89(2C), 129.14(2C), 132.02, 139.86, 145.22, 149.84, 153.51; MS (C₁₅H₁₃N₃), (m/z, %) = 263 (M⁺).

4-[(4-chlorophenyl)-diazenyl]-3-phenyl-1H-pyrazol-5-amine (7b)
Yield (78%); m.p. 230 °C; IR (KBr, ν cm⁻¹): 3335-3197(NH+NH₂); 1H NMR (DSMO-dš, ppm) δ 6.31 (s, 2H, D₂O-exchangeable, NH₂), 7.38-7.53 (m, 4H, Ar), 7.74 (t, J = 8.7 Hz, 3H (p, m, ph)), 8.10 (d, J = 8.5 Hz, 2H (o, ph), 12.11 (s, 1H, D₂O-exchangeable, NH); 13C NMR (DSMO-dš, ppm) 96.50, 126.27, 127.42, 127.99, 128.34, 128.47(2C), 128.83, 128.93, 129.15, 131.81, 132.90, 141.18, 145.47, 151.88; MS (C₁₅H₁₂ClN₃), (m/z, %) = 297 (M⁺, 35), 399 (M⁺+2, 11).

4-[(4-fluorophenyl)-diazenyl]-3-phenyl-1H-pyrazol-5-amine (7c)
Yield (70%); m.p. 225°C; IR (KBr, ν cm⁻¹): 3335-3200 (NH+NH₂); 1H NMR (DSMO-dš, ppm) δ 6.2 (s, 2H, D₂O-exchangeable, NH₂), 7.28-7.47 (m, 4H (m, o), Ar-), 7.77 (m, 3H (p, m) ph), 8.11 (d, J = 8.5 Hz, 2H (o, ph), 12.08 (s, 1H, D₂O-exchangeable, NH); 13C NMR (DSMO-dš, ppm) 95.60, 115.73, 116.04, 122.52, 122.57, 127.87, 128.26, 128.86, 130.55, 131.88, 133.02, 140.99, 147.42, 149.84, 154.40; MS (C₁₅H₁₂F₃N₃), (m/z, %) = 281 (M⁺).

Synthesis of 2,7-diphenyl-3-(phenyldiazenyl) pyrazolo[1,5-a] pyrimidine derivatives (10a-l)
A mixture of compound 7 (~ 0.3 g; 0.001 mol) and the corresponding enamines (8), (0.001 mol) in 20 ml CH₃COOH was refluxed for 1-2 h, left to cool. The product obtained was washed, dried, and crystallized from EtOH to give 10a-l compounds, respectively.

2,7-diphenyl-3-(phenyldiazenyl)pyrazolo[1,5-a]pyrimidine (10a)
Yield (72%); m.p. 190°C; IR (KBr, ν cm⁻¹): 1660 (C=N, 1H NMR (DSMO-dš, ppm) δ 7.45-7.65 (m, 10H.), 7.80 (d, J = 7.5 Hz, 2H), 8.15 (d, J = 6.5 Hz, 2H), 8.20 (d, J = 1.5 Hz, 2H), 8.86 (d, J = 4.5 Hz, 1H of pyrimidine); 13C NMR (DSMO-dš, ppm) 110.93, 120.85, 121.81, 128.63(2C), 128.69(2C), 129.45(2C), 129.50(2C), 129.59(2C), 129.99(2C), 131.50, 131.80, 139.62, 144.68, 146.13, 153.55, 153.78, 153.83; MS (C₂₃H₁₈N₄), (m/z, %) = 375 (M⁺).

7-[(4-chlorophenyl)-2-phenyl-3-(phenyldiazenyl)pyrazolo[1,5-a]pyrimidine (10b)
Yield (72%); m.p. 203°C; IR (KBr, ν cm⁻¹): 1665 (C=N, 1H NMR (DSMO-dš, ppm) δ 7.48-7.59 (m, 7H.), 7.70 (d, J = 8.1 Hz, 2H), 7.79 (d, J = 8.1 Hz, 2H), 8.16 (d, J = 7.5 Hz, 2H), 8.22 (d, J = 8.4 Hz, 2H), 8.87 (d, J = 4.2 Hz, 1H of pyrimidine); 13C NMR (DSMO-dš, ppm) 110.73, 120.56, 120.60, 121.63, 124.68, 128.46, 128.63, 129.27, 129.32(2C), 129.46(2C), 129.90(2C), 131.55 (2C), 131.67, 136.15, 139.44, 144.76, 153.28, 153.58, 153.62; MS (C₂₅H₁₆ClN₄), (m/z, %) = 409 (M⁺, 28), 411 (M⁺+2, 9).

2-phenyl-3-(phenyldiazenyl)-7-(p-tolyl)pyrazolo[1,5-a]pyrimidine (10c)
Yield (72%); m.p. 180°C; IR (KBr, ν cm⁻¹): 1664 (C=N, 1H NMR (DSMO-dš, ppm) δ 2.45 (s, 3H, CH₃) 7.46-7.60 (m, 9H.), 7.80 (d, J = 7 Hz, 2H), 8.13 (d, J = 8.1 Hz, 2H), 8.17 (d, J = 1.2 Hz, 2H ), 8.87 (d, J = 4.2 Hz, 1H of pyrimidine); 13C NMR (DSMO-dš, ppm) 20.97, 110.30, 120.62, 121.53(2C), 126.93, 128.38(2C), 129.05(2C), 129.20(2C), 129.24(2C), 129.34(2C), 129.68(2C), 129.75 (2C), 131.64, 141.50, 146.00, 153.51, 153.60; MS (C₂₇H₁₈N₄S), (m/z, %) = 389 (M⁺).

2-Phenyl-3-(phenyldiazenyl)-7-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidine (10d)
Yield (72%); m.p. 140°C; IR (KBr, ν cm⁻¹): 1668 (C=N, 1H NMR (DSMO-dš, ppm) δ 7.41-7.58 (m, 7H.), 7.81 (d, J = 1.5 Hz, 2H), 7.98 (d, J = 4.8 Hz, 1H), 8.20 (d, J = 4.8 Hz, 1H), 8.37 (d, J = 7.5 Hz, 2H), 8.60 (d, J = 3.6 Hz, 1H of pyrimidine), 8.82 (d, J = 4.8 Hz, 1H of pyrimidine); 13C NMR (DSMO-dš, ppm) 21.17, 743
3-(4-chlorophenyl)diazemyl)-2,7-diphenylpyrazolo[1,5-a]pyrimidine (10e)
Yield (72%), m.p. 170°C; IR (KBr, ν cm⁻¹): 3300, 2920, 1662, 1572, 1450, 1370, 1240, 1180, 1020, 770 (m/z, 100%); C NMR (DSMO-d6, ppm) δ 129.36(2C), 129.54(2C), 131.43(2C), 131.54(2C), 131.74(2C), 134.21, 136.21, 144.84, 152.16, 153.55, 161.26, 164.50 (C-F); MS (C₁₂₂H₁₀₂ClN₂S), (m/z, 100%) = 381 (M⁺).

7-(4-chlorophenyl)-3-((4-fluorophenyl)diazenyl)-2,7-diphenylpyrazolo[1,5-a]pyrimidine (10f)
Yield (72%), m.p. 160°C; IR (KBr, ν cm⁻¹): 3400, 2920, 1665, 1570, 1500, 1450, 1370, 1240, 1180, 1020, 770 (m/z, 100%); C NMR (DSMO-d6, ppm) δ 129.92(2C), 131.47(2C), 133.28, 134.27, 136.38, 144.48, 152.16, 153.55, 153.84; MS (C₂₃H₁₈ClN₅S), (m/z, 100%) = 409 (M⁺, 23), 411 (M⁺+2, 7).

7-(4-chlorophenyl)-3-(4-chlorophenyl)diazemyl)-2,7-diphenylpyrazolo[1,5-a]pyrimidine (10i)
Yield (72%), m.p. 120°C; IR (KBr, ν cm⁻¹): 3300, 2920, 1662, 1572, 1450, 1370, 1240, 1180, 1020, 770 (m/z, 100%); C NMR (DSMO-d6, ppm) δ 129.92(2C), 131.47(2C), 133.28, 134.27, 136.38, 144.48, 152.16, 153.55, 153.84; MS (C₂₃H₁₈ClN₅S), (m/z, 100%) = 409 (M⁺, 23), 411 (M⁺+2, 7).

7-(4-chlorophenyl)-3-((4-chlorophenyl)diazenyl)-2-phenylpyrazolo[1,5-a]pyrimidine (10j)
Yield (72%), m.p. 130°C; IR (KBr, ν cm⁻¹): 3300, 2920, 1662, 1572, 1450, 1370, 1240, 1180, 1020, 770 (m/z, 100%); C NMR (DSMO-d6, ppm) δ 129.36(2C), 129.54(2C), 131.43(2C), 131.54(2C), 134.21, 136.21, 144.48, 152.16, 153.55, 153.84; MS (C₂₃H₁₈ClN₅S), (m/z, 100%) = 409 (M⁺, 23), 411 (M⁺+2, 7).
3-((4-Fluorophenyl)diazenyl)-2-phenyl-7-(p-tolyl)pyrazolo[1,5-a]pyrimidine (12k)
Yield (72%), m.p. 203°C; IR (KBr, ν cm⁻¹): 3360 (NH), 1665 (C=N), 1370 (C=O); 1H NMR (DSMO-d6, ppm) δ 7.21-7.76 (m, 10H), 7.81 (d, J = 4.8 Hz, 2H), 7.96 (d, J = 4.8 Hz, 2H), 8.08 (d, J = 4.8 Hz, 1H, of pyrazolo), 12.45 (s, 1H, D-O-exchangeable, NH), 13C NMR (DSMO-d6, ppm) 98.15, 119.85, 125.41, 125.97, 127.12(2C), 128.22, 128.36(2C), 128.78(2C), 128.97(2C), 129.53(2C), 129.98(2C), 130.52(2C), 131.54(2C), 133.00, 135.20, 141.13, 144.86, 150.15, 152.70, 153.03, 161.23, 164.52, 171.99; MS (C₁₃H₁₄F₁₂N₄S), (m/z, 100%) = 363 (M⁺). 

Synthesis of 1H-imidazo[1,2-b]pyrazole Derivatives (12a–c)
For a mixture of compound 7a–c (0.26 g, 1 mmol), K₂CO₃ (0.45, 3mM) and compound 2 (0.357 g, 1 mmol) in acetonitrile (25 ml), the reaction mixture was refluxed for 4 h. and cooled at room temperature. The product was filtered, washed, dried, and recrystallized from EtOH to give 13a–b compounds, respectively.

2,6-Diphenyl-7-(phenyldiazenyl)-1H-imidazo[1,2-b]pyrazole (12a)
Yield (72%), m.p. 250°C; IR (KBr, ν cm⁻¹): 3360 (NH), 1665 (C=N), 1370 (C=O); 1H NMR (DSMO-d6, ppm) δ 7.15-7.65 (m, 10H), 7.17 (d, J = 4.8 Hz, 2H), 7.95 (d, J = 4.8 Hz, 2H), 8.45 (s, 1H of imidazo pyrazole), 12.32 (s, 1H, D-O-exchangeable, NH), 13C NMR (DSMO-d6, ppm) 98.13, 119.85, 125.41, 127.12(2C), 128.22, 128.36(2C), 128.78(2C), 128.97(2C), 129.53(2C), 129.98(2C), 130.52(2C), 131.11, 139.50, 141.27, 149.15; MS (C₁₃H₁₄N₄S), (m/z, 100%) = 363 (M⁺). 

General Procedure
The melting points were uncorrected and determined using an Electrothermal IA 9100 (Shimadzu, Japan) apparatus. Vario El-Mentar apparatus (Shimadzu, Japan), National Research Centre, Cairo, Egypt, carried out microanalytical research. IR spectra were reported on a Perkin-Elmer 1650 Spectrophotometer, National Research Centre, Cairo, Egypt as potassium bromide pellets using KBr disc technique. NMR experiments in Deuterated Dimethylsulfoxide (DMSO-d6) were calculated on a Varian -300 MHz and chemical changes were expressed as parts per million; ppm (δ values) against TMS as an internal standard, Faculty of Science, University of Cairo, Cairo, Egypt. Mass spectra were recorded on the 70 eV mass spectrometer at Shimadzu GCMS-QP-1000EX, University of Cairo, Cairo, Egypt.
Biological Evaluation
Cell Culture Conditions
The American Model Culture Collection (Rockville, MD) obtained the cells of human liver carcinoma (HepG-2), and human breast adenocarcinoma (MCF-7). The cytotoxicity activities on the lines of human cancer cells HepG-2 and MCF-7 were calculated using MTT assay, which was based on the reduction of tetrazolium salt in viable cells by mitochondrial dehydrogenases. The absorbance was measured at 570 nm, using a microplate reader from SpectraMax® Paradigm® Multi-Mode. The relative viability of the cells was expressed as the mean percentage of viable cells compared to the control cells not treated.

Statistical Analysis
Both tests were carried out in triplicate and replicated on three separate days. All the values were as mean ± SD. SPSS probit testing software system (SPSS Inc., Chicago, IL) calculated the IC50.

RESULTS AND DISCUSSION

Chemistry
In the first scheme, the phenacyl bromide was obtained by bromination of acetophenone, then reacted with KCN in dry benzene to afford compound 3, which allowed to reacting with 1-chloro-2-phenyldiazene (5) to yield compound 6, when it reacting with NH2.NH2.H2O yield 5-aminopyrazole derivatives (7a-c) The IR spectrum of compound 7a-c displayed the characteristic sharp absorption bands of NH and NH2 at ≈ 3335, 3200 cm-1, respectively (Scheme-1). The 1H-NMR spectrum of 7a-c exhibited the singlet signals of protons NH2 and NH appear at 6.2-6.31 and 12.08-12.11 ppm, respectively. 5-aminopyrazole derivatives (7a-c) as an intermediate key for synthesis the synthesis of compounds 10a-l and 12a-c derivatives as shown in Scheme-2, and 3.

Scheme-1: The Mechanistic Pathway for the Synthesis of 5-amino phenyldiazenyl-1H-pyrazol Derivatives (7a-c)

In Scheme-2, mating occurs between 5-amino phenyldiazenyl-1H-pyrazol (7a-c) and functionalized enaminoles (8) by refluxing in glacial CH3COOH, the addition of nucleophilic amino group to the olefinic double bond and releasing dimethylamine led to the formation of the corresponding pyrazolo [1-5a] pyrimidine (10a-l) (Scheme-2). The 1H-NMR spectrum of 10a-l exhibited the disappearance of the singlet as duplet signals at δ ≈ 8.17-8.56 and δ ≈ 8.85-8.90 ppm, respectively. The 13C-NMR spectrum of 10a-l
signals of protons NH₂ and NH and revealed deshielding of H-5, H-6 of pyrazolo [1-5a] pyrimidine appear exhibited a high chemical shift of F-C where it appears at about 164-171 ppm.

Also, 5-amino phenyldiazenyl-1H-pyrazole (7a-c) were refluxed with 2-bromo acetonaphone (2) in the presence of K₂CO₃ in acetone to afford the correspond imidazo[1,2-b]pyrazole derivatives (12a-c). The IR spectrum of compound 12a-c showed a sharp absorption band of NH at 3370 cm⁻¹. Also, the ¹H-NMR spectrum of 12a-c exhibited H protons of H-3 and NH of imidazo[1,2-b]pyrazole appear as singlet signals at δ ≈ 8.45-8.50 and δ ≈ 12.32-12.78 ppm, respectively (Scheme-3).

**Biological Activity**

**Cytotoxicity Activity**

The attained results showed that all compounds had dose-dependent cytotoxicity against both cell types. (Table-1, Figs.-2 and 3). The constructed deduction from these outcomes is that, in assessment with the positive control doxorubicin, compounds 7a-c with (IC₅₀ ≈ 29.4 µM) and 10e-d (IC₅₀ ≈ 29.9 µM) had comparable activities against HepG-2; compounds 10a, 10b, 10c, 10f, 10g, 10h, 10k, 10l, 12a and 12b had slightly moderate activities; compounds 12c, 10j and 10i, respectively, had fewer activities relative to the positive control, regarding human liver cancer (HepG-2) (Fig.-2 and Table-1). Regarding breast cancer cells (MCF-7); all the compounds were more potent relative to the positive control. In addition to 7a and 12a

| 10 | Ar₁ | Ar₂ |
|----|-----|-----|
| a  | Ph  | Ph  |
| b  | Ph  | 4-ClC₆H₄ |
| c  | Ph  | 4-MeC₆H₄ |
| d  | Ph  | 2-Thienyl |
| e  | 4-ClC₆H₄ | Ph |
| f  | 4-ClC₆H₄ | 4-ClC₆H₄ |
| g  | 4-ClC₆H₄ | 4-MeC₆H₄ |
| h  | 4-ClC₆H₄ | 2-Thienyl |
| i  | 4-FC₆H₄ | Ph |
| j  | 4-FC₆H₄ | 4-ClC₆H₄ |
| k  | 4-FC₆H₄ | 4-MeC₆H₄ |
| l  | 4-FC₆H₄ | 2-Thienyl |

Scheme-2: Synthesis of Phenylidazhenyl pyrazolo[1, 5-a]pyrimidine Derivatives (10a-l)
showed better anticancer activities against MCF-7 where \( \text{IC}_{50} \) for both compounds \( \approx 6.1 \ \mu M \) when compared with doxorubicin \( \text{IC}_{50} = 10.3 \ \mu M \) (Fig.-3 and Table-1).

\[
\begin{align*}
\text{Scheme-3: Synthesis of imidazo[1,2-b]pyrazole Derivatives (12a-c)}
\end{align*}
\]

Fig.-2: The Compounds had Anticancer Activity against the HepG-2 Human Cancer Cell Line at Various Concentrations

Fig.-3: The Compounds had Anticancer Activity against MCF-7 Human Cancer Cell Line at Various Concentrations

In general, from the SAR point of view, the pyrazolo [1-5a] pyrimidine and imidazo[1,2-b]pyrazole derivatives bearing phenyldiazenyl moiety have a significant anticancer agent. The combination of enaminoles and 2-bromoacetophenone with 5-aminopyrazole are given benefits. The activity of methyl group and 2-thiyl afford 10c-d which exhibited the highest anticancer activity against A549 cancer cell, respectively.
CONCLUSION

New pyrimidine and imidazo[1,2-b] pyrazole derivatives bearing phenyl diazenyl moiety were built and screened for anticancer activity. A few compounds exhibited good anticancer activities against HepG-2 and MCF-7. The compounds 7a-c and 10c-d are the most potont compound against MCF-7 cancer cells.

REFERENCES

1. R.M. Aly, R. A. Serya, A. M. El-Motwally, A. Esmat, S. Abbas and D.A. Abou El Ella, Bioorganic Chemistry 75, 368(2017), DOI:10.1016/j.bioorg.2017.10.018
2. S.A. Ahmed, A.M. Hussein and W.G. Hozayen, Journal of Heterocyclic Chemistry, 44, 803(2007), DOI:10.1002/jhet.5570440408
3. A. Gpalsamy, H. Yang, J.W. Ellingboe, H.R. Tsou, N. Zhang, E. Honores, D. Powell, M. Miranda, J.P. McGinnisb and S.K. Rabindran, Bioorganic and Medicinal Chemistry Letters, 15, 1591(2005), DOI:10.1016/j.bmcl.2005.01.066
4. J. Zhang, J.F. Peng, T. Wang, P. Wang and Z.T. Zhang, Journal of Molecular Structure, 1120, 228(2016), DOI:10.1016/j.molstruc.2016.05.026
5. A.M. Fahim and A.M. Farag, Journal of Molecular Structure 1199, 127025 (2020), DOI:10.1016/j.molstruc.2019.127025
6. M. S. Rao, T. B. Rao and C. P. Koteswara, Rasayan Journal of Chemistry 13(3), 1513(2020), DOI:10.31788/RJC.2020.1335799
7. P. S. Parmar and S. K. Patel, Rasayan Journal of Chemistry 13(3), 1555(2020), DOI:10.31788/RJC.2020.1335692
8. D. M. Sirsat, P. S. Bhale, H. V. Chavan, S. M. Karape and M. T. Bachute, Rasayan Journal of Chemistry 13, 1589(2020), DOI:10.31788/RJC.2020.1335768
9. V. P. Gilavali, P. K. Patel, H. K. Ram and J. H. Chauhan, Rasayan Journal of Chemistry, 13(4), 2249(2020), DOI:10.31788/RJC.2020.1346072
10. N. Petek, B. Štefane, M. Novinec and J. Svete, Bioorganic Chemistry 84, 226(2019), DOI:10.1016/j.bioorg.2018.11.029
11. G.M. Ali, D.A. Ibrahim, A.M. Elmetwalia and Ismail, Bioorganic Chemistry, 86, 1(2019), DOI:10.1016/j.bioorg.2019.01.008
12. P. Modi, S. Patel and M. Chhabria, *Bioorganic Chemistry*, **87**, 240(2019), DOI:10.1016/j.bioorg.2019.02.044
13. A. Stefano, A. Anna, B. Maurizio, T. Alessandra, O. Francesco, S. Silvia, B. Chiara and Y. Matilde, *ChemMedChem*, **5**, 1242(2010), DOI:10.1002/cmdc.201000165
14. A.E. Rashad, M.I. Hegab, R.E. Abdel-Megeid, J.A. Micky, and F.M. Abdel-Megeid, *Bioorganic and Medicinal Chemistry Letters*, **16**, 7102(2008), DOI:10.1016/j.bmcl.2008.06.054
15. D. Manetti, C. Brullo, M. Magnani, F. Mosci, B. Chelli, E. Crespan, S. Schenone, A. Naldini, O. Bruno and M.L. Trincavelli, *Journal of Medicinal Chemistry*, **51**, 1252(2008), DOI:10.1021/jm701240c
16. M. Radi, E. Dreassi, C. Brullo, E. Crespan, C. Tintori, V. Brenardo, M. Valoti, C. Zamperini, H. Daigi, F. Musumeci and F. Carraro, *Journal of Medicinal Chemistry*, **54**, 2610(2011), DOI:10.1021/jm1012819
17. A.S. Hassan, A.F. Mady, H.M. Awad and T.S. Hafez, *Chinese Chemical Letters*, **28**, 388(2017), DOI:10.1016/j.cclet.2016.10.022
18. A.S. Hassan, T.S. Hafez, S.A. Osman and M.M. Ali, *Turkish Journal of Chemistry*, **39**, 1102(2015), DOI:10.3906/kim-1504-12
19. N.S. Ismail, G.M. Ali, D.A. Ibrahim and A.M. Elmetwali, *Future Journal of Pharmaceutical Science*, **2**, 60(2016), DOI:10.1016/j.fjps.2016.08.004
20. N.R. Kumar, Y. Poornachandra, D.K. Swaroop, G.J. Dev, C.G. Kumar and B. Narsaiah, *Bioorganic and Medicinal Chemistry Letters*, **26**, 5203(2016), DOI:10.1016/j.bmcl.2016.09.062
21. O.M. Ahmed, M.A. Mohamed, R.R. Ahmed and S.A. Ahmed, *European Journal of Medicinal Chemistry*, **44**, 3519(2009), DOI:10.1016/j.ejmech.2009.03.042
22. E.K. Abdelall and J.N. Philoppes, ARKIVOK v, 210 (2016), DOI:10.3998/ark.5550190.p009.743
23. T.A. Farghaly and A.S. Shawali *Tetrahedron*, **66**, 2700 (2010), DOI:10.1016/j.tet.2013.03.103
24. A. Rahmati, M.E. Vashareh and M.A. Kouzehrash, *Tetrahedron*, **69**, 4199(2013), DOI:10.1016/j.tet.2013.03.103
25. J. Khalafy, A.P. Marjani F. Salami. *Tetrahedron Letters*, **55**, 6671(2014), DOI:10.1016/j.tetlet.2014.10.061
26. A.T. Baviskar, C. Madaan, R. Preet, P. Mohapatra, V. Jain, A. Agarwal, S.K. Guchhait, C.N. Kundu, U.C. Banerjee and P.V. Bharatam, *Journal of Medicinal Chemistry*, **54**, 5013(2011), DOI:10.1021/jm200235u
27. S. Grosse, V. Mathieu, C. Pillard, S. Massip, M. Marchivie, C. Jarry, P. Bernard, R. Kiss and G. Guillaumet, *European Journal of Medicinal Chemistry*, **84**, 718(2014), DOI:10.1016/j.ejmech.2014.07.057
28. A.F. Kassem, I.F. Nassar, M.T. Abdel-Aal, H.M. Awad and W.A. El-Sayed, *Chemical and Pharmaceutical Bulletin*, **67**, 888(2019), DOI:10.1248/cpb.c19-00280
29. F.M. Almonderej, H.H. Elganzory, M.N. El-Bayaa, H.M. Awad and W.A. El-Sayed, *Molecules*, **24**, 3738(2019), DOI:10.3390/molecules24203738
30. M.E. Haiba, E.S. Al-Abdullah, N.S. Ahmed, H.A. Ghabbour, H.M. Awad, *Journal of Molecular Structure*, **1195**, 702(2019), DOI:10.1016/j.molstruc.2019.05.081

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