Journal of Applied Pharmaceutical Science Vol. 10(09), pp 012-022, September, 2020
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2020.10902
ISSN 2231-3354

One-pot three-component synthesis of new triazolopyrimidine derivatives bearing indole moiety as antiproliferative agents

Mohamed A. A. Radwan[1,2*], Fahad M. Alminderej[1], Hala E. M. Tolan[3], Hanem M. Awad[4]

[1]Department of Chemistry, College of Science, Qassim University, Buraydah, Kingdom of Saudi Arabia.
[2]Applied Organic Chemistry Department, National Research Center, Dokki, 12622, Egypt.
[3]Department of Photochemistry, National Research Centre, Dokki, 12622, Cairo, Egypt.
[4]Tanning Materials and Leather Technology Department, National Research Centre, Dokki, Cairo, 12311, Egypt.

ARTICLE INFO

Received on: 28/03/2020
Accepted on: 18/07/2020
Available online: 05/09/2020

Key words:
Triazole, pyrimidine, indole, multicomponent reaction, antiproliferative.

ABSTRACT

A new series of triazolopyrimidine derivatives was produced via three-component reactions of suitable aromatic or heteroaromatic carboxaldehyde, 3-amino-1,2,4-triazole, and 3-indolyl-3-oxopropanenitrile in triethylamine as a catalyst. The new compounds have been interpreted using elemental analysis, infrared, mass spectrometry, and nuclear magnetic resonance spectroscopy. Antiproliferative effects of the new compounds have been screened on four human cancer types and one human noncancerous type (retinal pigment ephitilial-1) via the 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide assay. Compounds **4a** and **4h** have moderate activity against the human colon cancer; most of the compounds were active toward human lung cancer; compounds **4i**, **4h**, and **4g** were highly active on hormone-dependent human breast cancer, while compounds **4c**, **4b**, **4h**, and **4e** were the most active on the hormone-independent human breast. The results of this study offer a source for further investigation of selected triazolopyrimidine derivatives as antiproliferative agents.

INTRODUCTION

The construction of both scaffolds triazole and pyrimidine rings with a built-in indole moiety might have promising biological activity. Multicomponent reactions (MCRs) are a wide range of synthetic techniques that can be used to achieve this target candidate (Cioc *et al*., 2014; Dekamin *et al*., 2013; Liu *et al*., 2016; Peng *et al*., 2017; Ravichandiran *et al*., 2017; Rotstein *et al*., 2014). Compared to the direct synthesis method, the MCR method is appreciated for its cost-effectiveness, ease of set-up, and high production. Currently, many nitrogen heterocyclic structures (mainly indole units with multiple biological activities) are prepared by MCRs (Allen *et al*., 2017; Anand *et al*., 2017; Carbajales *et al*., 2017; Gribble, 2000). The unique indole backbone is considered to be the most widespread compound that is common in medical advances. Similarly, an indole is a substructure of many natural medical activities (Gribble, 2010). In addition, several indole compounds have attracted more consideration owing to their biological properties, such as their antimicrobial, anticancer, and antiviral activities (Bao *et al*., 2005; Endo *et al*., 2007; Sakemi and Sun, 1991; Yang *et al*., 2004). In such an indole, a framework, triazole (Duran *et al*., 2002; Gujjar *et al*., 2009; Holla *et al*., 2005; Sztanke *et al*., 2008) and pyrimidine (Kim *et al*., 2012; Selvaraj and Rajesh, 2016) ring, is well identified as the key structure of several therapeutic scaffolds as they display diverse bioactivities. Fused heterocycles are widely considered due to their share in the different steps of drug discovery, and they often function as basic central units in many therapeutic chemistry programs (Coxon *et al*., 2017; Taylor *et al*., 2014). Among them, the triazolopyrimidinone unit, a purine analog, is well known for displaying some biological activities, such as anti-inflammatory activity, ulcerogenic properties, serotonin antagonist, analgesic, antimicrobial, antifungal, cytotoxic, and antitumor activities (Boechat *et al*., 2012; Hafez *et al*., 2008; Huang *et al*., 2012; Lakamoska *et al*., 2009; Wang *et al*., 2017; Zhang *et al*., 2007; Zhao *et al*., 2007). Moreover, triazolopyrimidines have the greatest valuable construction base for the synthesis of bioactive drugs (Fig. 1) (Łakomska *et al*., 2013), which possess many pharmacological measures, such as antitumor (Marwaha *et al*., 2012), antimalarial (Luo *et al*., 2013), antimicrobial, (Abdel-Aziem *et al*., 2012),

*Corresponding Author
Mohamed A. A. Radwan, Applied Organic Chemistry Department, National Research Center, Dokki, 12622, Egypt; National Research Centre, Cairo, Egypt. E-mail: m1radwan @ yahoo.com

and anti-inflammatory activities (Khera *et al*., 2011), inhibition of the kinase insert domain-covering receptor (kill/death ratio kinase) (Ashour *et al*., 2013), and antifungal properties (Chen *et al*., 2008). They are known to show anticancer, anti-Alzheimer's, antihypertensive, leishmanicidal cardiac stimulant, antipyretic, potential herbicidal, and anti-HBV activities (Gujjar *et al*., 2009). The previous biological history of triazolopyrimidine is evident in Trapidil (Fischer, 2008) and Cevipabulin (El-Gendy *et al.*, 2008). Recently, triazolopyrimidines have been realized to modify AChE inhibition, amyloid β-aggregation inhibition, anti-inflammation, and are noted as a probable anti-Alzheimer's agent (Kumar *et al*., 2016). Generally, heterocyclic compounds have many applications (Adole *et al*., 2019, 2020; Bisht *et al*., 2018; Chobe *et al*., 2014; Kamble *et al*., 2016). As an extension of our work regarding the direction on the synthesis of bioactive indolyl molecules (El-Nezhawy *et al*., 2016, 2009a, 2009b; Fakhr *et al*., 2004, 2009; Ghorab *et al*., 2008; Muhammad *et al*., 2019; Radwan and El-Sherbiny, 2007; Radwan and Eman, 2009; Radwan *et al*., 2007; Radwan *et al*., 2009a, 2009b, 2020) (Fig. 2), we describe herein a multicomponent synthesis and antitumor estimation of the novel triazolopyrimidine-6-carbonitrile derivatives via the reaction of 3-aminotriazole, suitable aldehydes, and 3-cyanoacetyl indole.

MATERIALS AND METHODS

Chemicals were obtained from Merck and Sigma-Aldrich. Melting point (°C) was measured on the XT-5 microscopic apparatus. C, H, and N analyses and infrared (IR) spectra, which were measured using an iS10 spectrometer (ν in cm^{-1}) using KBr disk, were carried out at Cairo University. MS (EI) *m/z* analysis was carried out via a Thermo Scientific DCQII. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) were carried out in dimethyl sulfoxide (DMSO-d_6) on a Bruker (400 MHz) Ascend - Magnets | Bruker spectrometer.

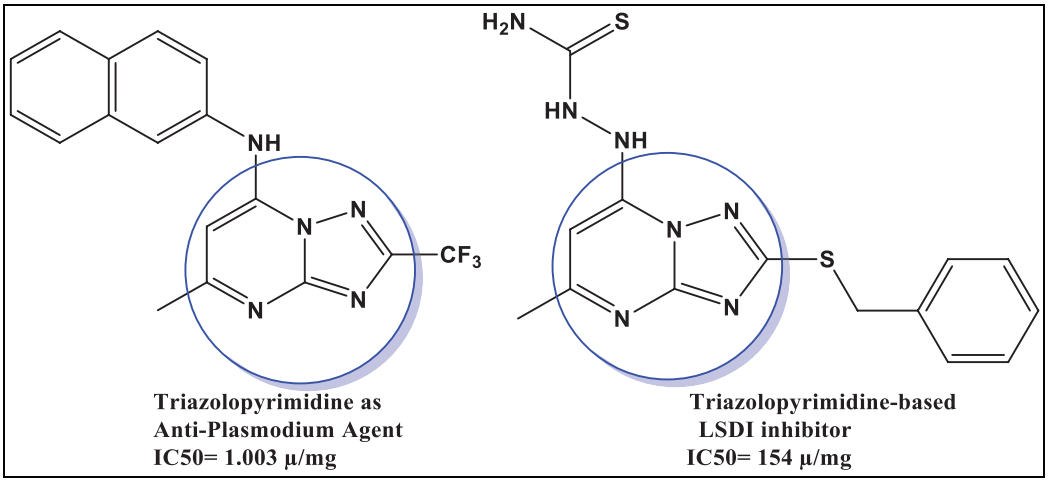


Figure 1. Biological activity of some of the triazolopyrimidine compounds.

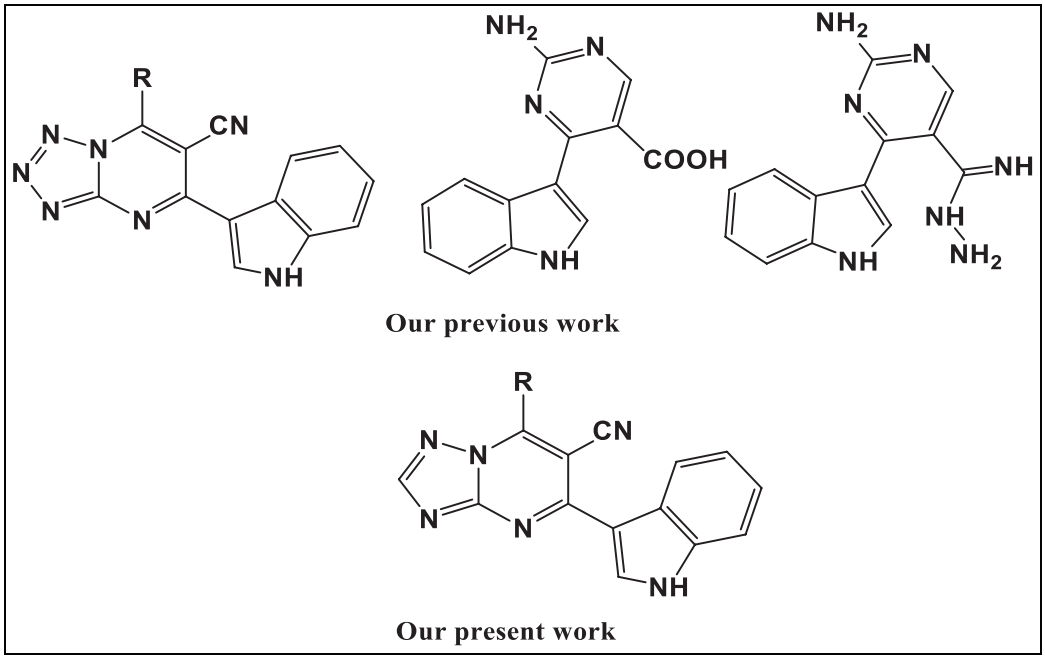


Figure 2. Some of our previous and present works bearing indole moiety.

Synthesis of 7-substituted-5-(1H-indol-3-yl)-[1,2,4]triazolo [1,5-a]pyrimidine-6-carbonitrile 4a-i

General method

Triethylamine (0.5 mmol) was added to a mixture of aldehydes (1 mmol), 3-amino-1,2,4-triazole (1 mmol), and 3-cyanoacetyl-indole (1 mmol) in dimethyl-formamide (DMF) (5 ml), and heated at 120ºC for about 10 hours (observed by thin layer chromatography). Then, the mixture was cooled and the precipitate was recrystallized from Ethanol/Dimethyl-Formamide (EtOH/DMF).

7-(4-Chlorophenyl)-5-(1H-indol-3-yl)-[1,2,4]triazolo[1,5-a] pyrimidine-6-carbonitrile (4a)

Yield 76%; mp 281°C–3°C. IR (KBr, cm^{-1}): 3,312 (NH), 2,212 (CN). ^{1}H NMR (DMSO-d_6) δ/ppm: 7.23–7.27 (m, 2H, indole H-5, H-6), 7.51–7.53 (dd, *J* = 1.1, 8.4 Hz, 1H, indole H-7), 7.63–7.64 (d, *J* = 7.6 Hz, 2H, Ph), 8.03–8.04 (d, *J* = 7.6 Hz, 2H, Ph), 8.13 (dd, *J* = 1.1, 8.4 Hz, 1H, indole H4), 8.20 (s, 1H, triazole), 8.43 (s, 1H, indole-H2), 12.30 (brs, NH); ^{13}C NMR (DMSO-d_6) δ/ppm: 153.08, 149.44, 138.76, 136.72, 136.30, 131.34, 129.23, 126.04, 123.60, 122.46, 121.30, 117.38, 113.48, 112.49, 112.09; **MS** (EI) *m/z* %: 371 [M^++1]. Anal. calcd. for $C_{20}H_{11}ClN_6$: C, 64.78; H, 2.99; N, 22.67. Found: C, 64.89; H, 2.91; N, 22.61.

5-(1H-Indol-3-yl)-7-(4-nitrophenyl)-[1,2,4]triazolo[1,5-a] pyrimidine-6-carbonitrile (4b)

Yield 76%; mp 288°C–9°C. IR (KBr, cm^{-1}): 3,232 (NH), 2,223 (CN). ^{1}H NMR (DMSO-d6) δ/ppm: 7.23–7.28 (m, 2H, indole H5, H6), 7.52 (dd, *J* = 1.1, 8.6 Hz, 1H, indole H7), 8.14 (dd, *J* = 1.1, 8.4 Hz, 1H, indole H4), 8.16–8.20 (dd, *J* = 1.1, 8.1 Hz, 2H, Ph), 8.31 (s, 1H, triazole), 8.36–8.38 (dd, *J* = 1.1, 8.1 Hz, 2H, Ph), 8.47 (s, 1H, indole-H2), 12.33 (brs, NH); ^{13}C NMR (DMSO-d6) δ/ppm: 153.33, 147.66, 139.62, 135.90, 136.79, 132.13, 131.10, 125.95, 124.04, 122.62, 121.31, 116.76, 115.10, 113.42, 112.54; **MS** (EI) *m/z* (%) 383 [M^++2]. Anal. calcd. for $C_{20}H_{11}N_7O_2$: C, 62.99; H, 2.91; N, 25.71. Found: C, 63.12; H, 2.93; N, 25.45.

7-(4-Bromophenyl)-5-(1H-indol-3-yl)-[1,2,4]triazolo[1,5-a] pyrimidine-6-carbonitrile (4c)

Yield 74%; mp 279°C–81°C. IR (KBr, cm^{-1}): 3,232 (NH), 2,223 (CN). ^{1}H NMR (DMSO-d_6) δ/ppm: 7.23–7.26 (m, 2H, indole H5, H6), 7.50 (dd, *J* = 1.1, 8.3 Hz, 1H, indole H7), 7.62–7.64 (dd, *J* = 7.8 Hz, 2H, Ph), 8.02–8.03 (dd, *J* = 7.8 Hz, 2H, Ph), 8.12 (dd, *J* = 1.1, 8.3 Hz, 1H, indole H4), 8.21 (s, 1H, triazole), 8.44 (s, 1H, indole-H2), 12.28 (brs, NH); ^{13}C NMR (DMSO-d_6) δ/ppm: 151.72, 147.12, 137.74, 135.30, 132.18, 132.00, 131.64, 126.02, 125.85, 123.61, 122.45, 121.32, 117.40, 112.51, 112.12; **MS** (EI) *m/z* (%) 414 [M^+, 4]; 3,286 (NH), 2,204 (CN). Anal. calcd. for $C_{20}H_{11}BrN_6$: C, 57.85; H, 2.67; N, 20.24. Found: C, 57.90; H, 2.63; N, 20.19.

7-(2-Hydroxyphenyl)-5-(1H-indol-3-yl)-[1,2,4]triazolo[1,5-a] pyrimidine-6-carbonitrile (4d)

Yield 67%; mp 271°C–3°C. IR (KBr, cm^{-1}): 3,210–3,324 (OH and NH), 2,210 (CN). ^{1}H NMR (DMSO-d_6) δ/ppm: 7.21–7.27 (m, 2H, indole H5, H6), 7.32–7.39 (m, 4H, Ph), 7.48 (dd, *J* = 1.1, 8.1 Hz, 1H, indole H7), 7.96–7.99 (dd, 2H, dd, *J* = 1.1, 8.1 Hz, 1H, indole H4), 8.23 (s, 1H, triazole), 8.41 (s, 1H, indole-H2), 12.19 (s, OH), 12.24 (s, NH); ^{13}C NMR (DMSO-d_6) δ/ppm: 155.12, 153.67, 148.36, 141.23, 137.87, 136.90, 135.41, 133.16, 131.27, 126.54, 123.69, 122.74, 121.77, 117.90, 113.56, 112.61, 112.13; **MS** (EI) *m/z* (%) 352 [M^+]. Anal. calcd. for $C_{20}H_{12}N_6O$: C, 68.18; H, 3.43; N, 23.85. Found: C, 68.25; H, 3.21; N, 23.81.

5-(1H-Indol-3-yl)-7-(2-nitrophenyl)-[1,2,4]triazolo[1,5-a] pyrimidine-6-carbonitrile (4e)

Yield 70%; mp 291°C–3°C. IR (KBr, cm^{-1}): 3,202 (NH), 2,206 (CN). ^{1}H NMR (DMSO-d_6) δ/ppm: 7.29–7.36 (m, 2H, indole H5, H6), 7.47 (dd, *J* = 1.1, 8.2 Hz, 1H, indole H7), 7.73–7.78 (m, 2H, Ph), 7.96–7.98 (m, 2H, Ph), 8.02–8.03 (dd, *J* = 1.1, 8.2 Hz, 1H, indole H4), 8.24 (s, 1H, triazole), 8.40 (s, 1H, indole-H2), 12.24, (s, NH); ^{13}C NMR (DMSO-d_6) δ/ppm: 150.98, 146.82, 145.66, 138.65, 137.96, 135.92, 135.31, 132.36, 128.22, 127.02, 124.63, 123.47, 122.31, 118.37, 114.49, 112.11, 111.95. **MS** (EI) *m/z* (%) 384 [M^++2]. Anal. calcd. for $C_{20}H_{11}N_7O_2$: C, 62.99; H, 2.91; N, 25.71. Found: C, 63.17; H, 2.90; N, 25.41.

5-(1H-Indol-3-yl)-7-(thiophen-2-yl)-[1,2,4]triazolo[1,5-a] pyrimidine-6-carbonitrile (4f)

Yield 64%; mp 266°C–8°C. IR (KBr, cm^{-1}): 3,245 (NH), 2,213 (CN). ^{1}H NMR (DMSO-d_6) δ/ppm: 7.20–7.23 (m, 2H, thiophene), 7.31–7.32 (m, 2H, indole H5, H6), 7.46 (dd, *J* = 1.1, 8.4 Hz, 1H, indole H7), 7.53 (s, 1H, thiophene), 7.99–8.03 (dd, *J* = 1.1, 8.4 Hz, 1H, indole H4), 8.26 (s, 1H, triazole), 8.45 (s, 1H, indole-H2), 12.28, (s, NH); ^{13}C NMR (DMSO-d_6) δ/ppm: 146.40, 137.76, 135.52, 134.38, 134.21, 129.51, 127.12 124.50, 123.31, 122.42, 117.14, 114.73, 113.44, 107.65; **MS** (EI) *m/z* (%) 342 [M^+]. Anal. calcd. for $C_{18}H_{10}N_6S$: C, 63.15; H, 2.94; N, 24.55; S, 9.36. Found: C, 63.21; H, 2.91; N, 24.52; S, 9.34.

7-(Furan-2-yl)-5-(1H-indol-3-yl)-[1,2,4]triazolo[1,5-a] pyrimidine-6-carbonitrile (4g)

Yield 64%; mp 269°C–71°C. IR (KBr, cm^{-1}): 3,232 (NH), 2,214 (CN). ^{1}H NMR (DMSO-d_6) δ/ppm: 7.11(m, 1H, furan), 7.32–7.34 (m, 2H, indole H5, H6), 7.47 (dd, *J* = 1.1, 8.5 Hz, 1H, indole H7), 7.51(m, 1H, furan), 7.98 (m, 1H, furan), 8.02–8.03 (dd, *J* = 1.1, 8.5 Hz, 1H, indole H4), 8.22 (s, 1H, triazole), 8.43 (s, 1H, indole-H2), 12.17 (s, NH); ^{13}C NMR (DMSO-d_6) δ/ppm: 149.80, 147.64, 138.46, 136.12, 127.20, 124.50, 123.30, 121.32, 120.41, 118.74, 115.01, 114.64, 113.44, 106.72. **MS** (EI) *m/z* (%) 326 [M^+]. Anal. calcd. for $C_{18}H_{10}N_6O$: C, 66.25; H, 3.09; N, 25.75. Found C, 66.31; H, 3.01; N, 25.83.

5-(1H-Indol-3-yl)-7-(1H-pyrrol-2-yl)-[1,2,4]triazolo[1,5-a] pyrimidine-6-carbonitrile (4h)

Yield 67%; mp 258°C–61°C. IR (KBr, cm^{-1}): 3,221 (NH), 2,216 (CN). ^{1}H NMR (DMSO-d_6) δ/ppm: 6.21–6.23 (m, 1H, pyrrole-H3), 6.51–6.52 (d, 1H, pyrrole-H4), 7.02–7.03 (d, 1H, pyrrole-H2), 7.31–7.34 (m, 2H, indole H5, H6), 7.43 (dd, *J* = 1.1, 8.6 Hz, 1H, indole H7), 8.01–8.02 (dd, *J* = 1.1, 8.6 Hz, 1H, indole H4), 8.20 (s, 1H, triazole), 8.41 (s, 1H, indole-H2), 11.64 (s, NH), 12.11 (s, NH); ^{13}C NMR (DMSO-d_6) δ/ppm: 145.97, 144.34, 137.86, 136.12, 127.13, 124.43, 123.30, 123.08, 122.11, 118.06, 114.36, 113.88, 111.20, 105.01; **MS** (EI) *m/z* (%) 327 [M^++2].

Anal. calcd. for $C_{18}H_{11}N_7$: C, 66.45; H, 3.41; N, 30.14. Found: C, 66.53; H, 3.37; N, 30.12.

5,7-di(1H-Indol-3-yl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carbonitrile (4i)

Yield 61%; mp 296°C–8°C. IR (KBr, cm^{-1}): 3,236–3,265 (2NH), 2,206(CN). ^1H NMR (DMSO-d_6) δ/ppm: 7.31–7.35 (m, 4H, di-indole H5, H6), 7.48 (dd, J = 1.1, 8.1 Hz, 2H, di-indole H7), 8.01–8.02 (dd, J = 1.1, 8.1 Hz, 2H, di-indole H4), 8.18 (s, 1H, triazole), 8.31, 8.32 (ss, 2H, indole-H2), 12.21 (s, NH), 12.23 (s, NH); ^{13}C NMR (DMSO-d_6) δ/ppm: 152.06, 151.52 137.81, 137.74, 135.31, 132.33, 131.10, 128.24, 127.03, 124.95, 124.61, 123.47, 122.31, 118.39, 114.47, 112.23, 111.16; **MS** (EI) *m/z* (%) 375 [M^+]. Anal. calcd. for $C_{22}H_{13}N_7$: C, 70.39; H, 3.49; N, 26.12. Found: C, 70.45; H, 3.42; N, 26.10.

In vitro *cell culture*

The human colorectal carcinoma (HCT-116) and human breast adenocarcinoma (MCF-7), (MDA-MB-231), and (A549) cell lines were acquired from the American Type Culture Collection (ATCC, Rockville, MD) and preserved in the DMEM-F12 medium which was complemented with 10% heat-inactivated fetal bovine serum, 100 U/ml penicillin, and 100 U/ml streptomycin. The cells were grown at 37°C in a moistened atmosphere of 5% CO_2.

3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) antiproliferative assay

The antiproliferative activity on HCT-116, MCF-7, MDA-MB-231, and A549 human cancer cells and retinal pigment ephitilial-1 (RPE-1) human normal cells was assessed by the MTT assay, which depends on the reduction of the tetrazolium salt by mitochondrial dehydrogenases in feasible cells (Ashraf *et al*., 2017; Emam *et al*., 2017; Eman *et al*., 2017). Cells were first distributed in a 96-well sterile microplate (2×10^4 cells/well) and incubated at 37°C in DMSO with diverse concentrations of each established compound or doxorubicin for 48 hours in a serum-free medium. After incubation, the media were carefully discarded, and 40 µl of MTT (2.5 mg/ml) was added to individual wells and then incubated for an extra 4 hours. The purple formazan dye crystals were solubilized by adding 200 µl of DMSO. The absorbance was measured at 570 nm via a SpectraMax Paradigm multimode microplate reader. The comparative cell viability was stated as the mean ratio of viable cells related to the unprocessed control cells. All trials were conducted in triplicate and repeated on three diverse days. The values were signified as mean ± SD. The efficacious doses for 50% of the cancerous cells population (ED_{50}) and their toxic doses in 50% of the noncancerous cells population were evaluated by Probit analysis by the Statistical Package for the Social Sciences (IBM Corp., Armonk, NY).

RESULTS AND DISCUSSION

Chemistry

The strategy in the presented work is the synthesis of a new series of triazolopyrimidine derivatives via an MCR of proper carboxaldehydes **1**, 3-amino-1,2,4-triazole **2**, and 3-indolyl-3-oxopropanenitrile **3** (Scheme 1 and Scheme 2).

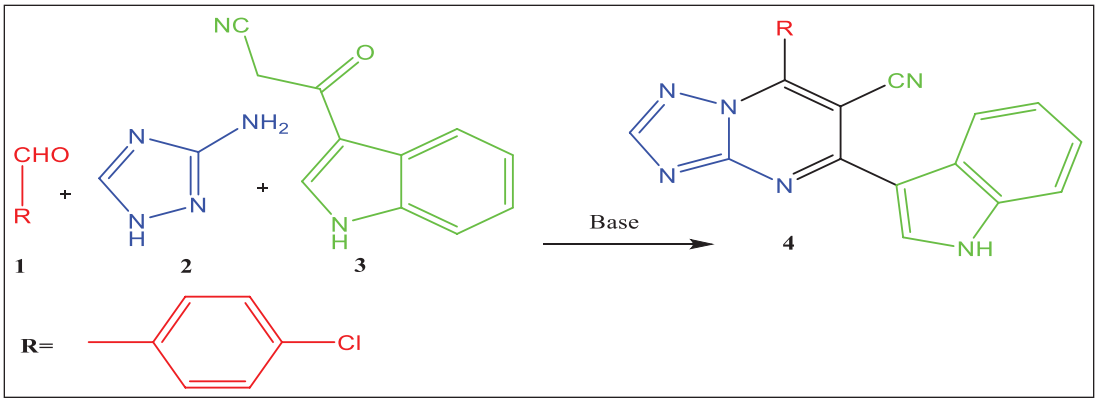
The MCR was carried out in the presence of different solvents and bases to check the effect on the rate of reaction and to find out the standard optimized reaction conditions

When the MCR was completed in ethanol without a catalyst, despite heating for 12 hours (Table 1, entry 1), there was no product formation.

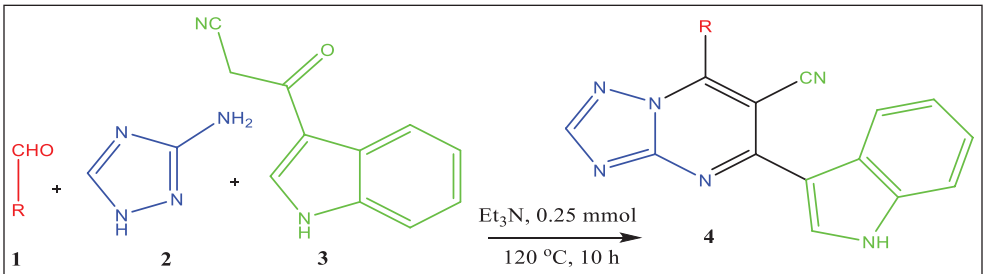
Subsequently, we catalyzed a reaction by triethylamine in different solvents (Table 1, entries 1–6). Then, we studied the reactions in various basic conditions (Table 1, entries 7–12). The reaction results showed that organic bases gave good results, while the yield of the reaction in the presence of inorganic strong bases, like KOH and NaOH, is not satisfactory. Surprisingly, K_2CO_3 did not furnish the product.In conclusion, the best condition for this reaction is to soak in DMF in 0.25 mol triethylamine for 10 hours at 120°C (Table 1, entry 6).

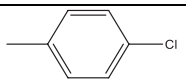
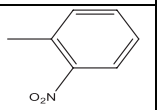
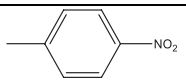
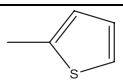
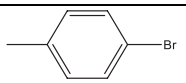
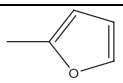
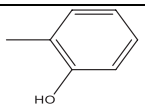
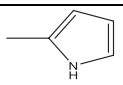
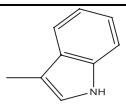
As a result of the overhead reaction, a possible mechanism was proposed for the construction of triazolopyrimidine. First, triethylamine activated the nucleophilic reaction of 3-indolyl-3-oxopropanenitrile **3** via hydrogen bonding to excite carboxaldehyde **1**. The initiation of carboxaldehyde by H-bond enhances the electrophilicity of the carboxaldehyde and improves the building of a transitional **A** (Reddi *et al*., 2015). Intermediate **A** and 3-amino-1,2,4-triazole **2** then undergo Michael's reaction to form intermediate **B** via intramolecular cyclization reaction to form a C–N bond. Subsequently, compound **4** was obtained by autoxidation (Scheme 3).

The structure of the newly synthesized compounds (**4a–i**) was identified via the interpretation of spectral studies and mass analysis (experimental units), e.g., the IR of compound **4a**



Scheme 1. Synthesis of triazolopyrimidine under different conditions of base, solvent, temperature, and time.

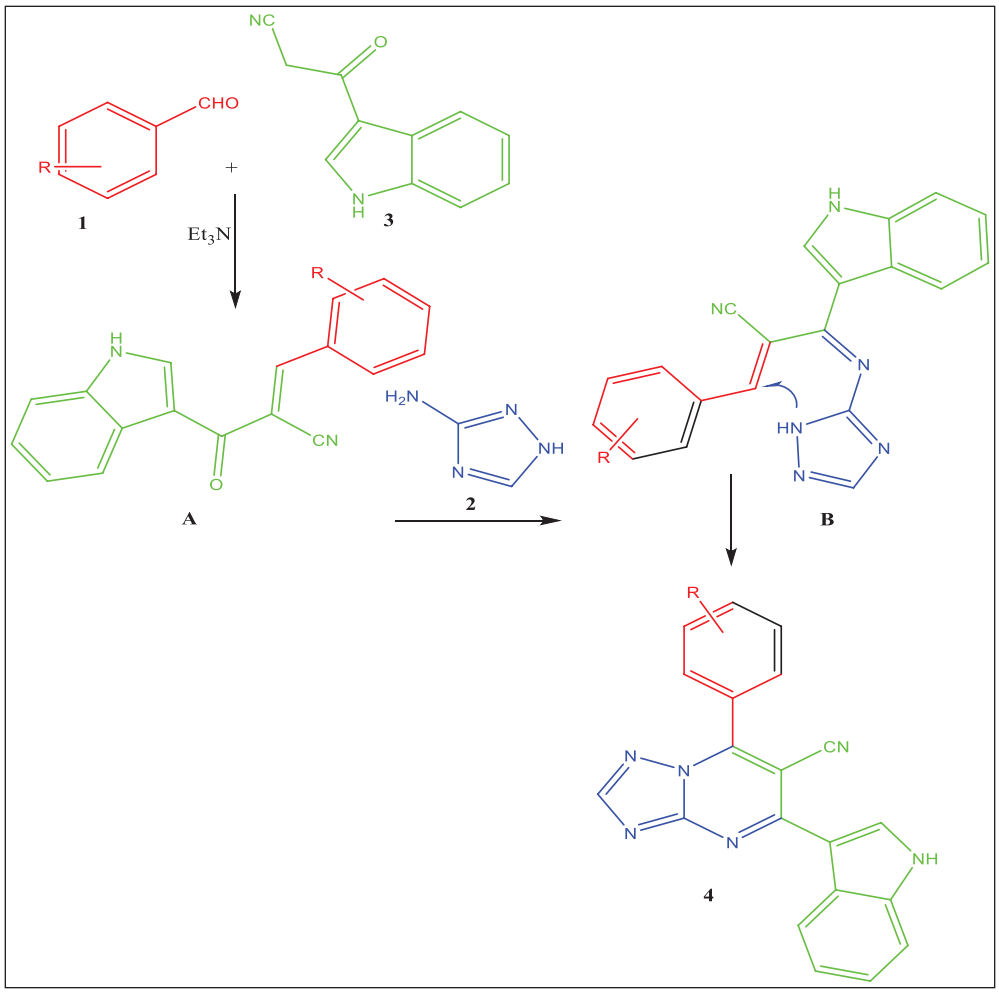


Compound	R	Compound	R
4a		**4e**	
4b		**4f**	
4c		**4g**	
4d		**4h**	
4i			

Scheme 2. Reaction conditions: aldehyde 1 (1 mmol), 3-amino-1,2,4-triazole 2 (1 mmol), 3-cyanoacetyl indole **3** (1 mmol), and Et_3N (0.25 mmol), in DMF at 120°C, 10 hours.

Table 1. Optimization of the reaction conditions for the synthesis of triazolopyrimidine derivatives **4a**.

Entry	Solvent	Alkali (mmol)	Temp. (°C)	Time (hours)	Yield (%)
1	EtOH	0	80	12	0
2	EtOH	Et_3N	80	10	Trace
3	CH_3CN	Et_3N	80	10	17
4	1,4-Dioxane	Et_3N	80	10	11
5	Toluene	Et_3N	120	10	0
6	DMF	Et_3N	120	10	79
7	DMF	Piperidine (0.5)	120	10	66
8	DMF	DMAP (0.2)	120	10	33
9	DMF	Pyridine	120	10	37
10	CH_3CN	KOH	80	8	20
11	CH_3CN	NaOH	80	8	24
12	CH_3CN	K2CO3	80	8	Trace



Scheme 3. Proposed mechanism of three-component reactions.

exposed bands at 3,312 and 2,212 cm^{-1} for the NH and cyano functions, respectively, along with the disappearance of NH_2 and C=O groups. Furthermore, ^1H NMR showed a broad peak (exchangeable D_2O) at 12.27 ppm of the −NH group, a single peak at 8.20 ppm of the triazole proton, and aromatic signals at 7.23–8.43 ppm. Also, ^{13}C NMR data and mass reinforced a proposed structure for **4a** (*m/z* 370, M+).

Antiproliferative screening

According to the revealed synthetic route, a series of the obtained triazolopyrimidines (**4a**–**4i**) was selected for further investigation of their antiproliferative activities *in vitro* on four human cancer types along with their cytotoxic effects on one nontumorous human healthy type RPE-1 by the MTT test. The proportion of live cells was evaluated and correlated with the control and reference drug doxorubicin. All compounds repressed the five human cell types (Figs. 3–7). In the HCT-116, Table 2 and Figure 3 demonstrate that compounds **4a** and **4h** had close antiproliferative effects, and the remaining compounds had significantly fewer antiproliferative activities than doxorubicin. While, in the MCF-7, compounds **4i** and **4h** had a more potent effect, compound **4g** had a comparable activity and the rest of the compounds had less antiproliferative properties relative to doxorubicin (Fig. 4 and Table 2). For MDA-MB-231 human breast cancer, compounds **4c** and **4b** had a more potent effect; compounds **4h** and **4e** had equipotent effects; and compounds **4d**, **4a**, **4g**, **4f**, and **4i** had significantly less antiproliferative effects related to doxorubicin (Fig. 5 and Table 2). For A549 cancer, compounds **4d**, **4i**, **4e**, **4f**, **4g**, and **4h** had extra antiproliferative actions and compounds **4b**, **4c**, and **4a** had insignificantly lesser antiproliferative effects than doxorubicin (Fig. 6 and Table 2). In the nontumorous human healthy normal cells (RPE-1), compounds **4f**, **4g**, and **4e** were more toxic; three compounds **4a**, **4i**, and **4d** had insignificant toxic effects; and three compounds **4c**, **4b**, and, **4h** had significant toxic effects related to the reference drug.

These results indicated that all the prepared candidates are effective anticancer compounds in human lung cancer, except for compound **4a**, which had significantly less activity; compound **4h** had an effective antiproliferative activity on all cancerous types and had the least toxic effect on the noncancerous cells; and compound **4i** had the best antiproliferative effect on both MCF-7 and A549 cancerous types, while having a weak antiproliferative effect on both HCT-116 and MDA-MB-231 cancerous types; compounds **4i**, **4h**, and **4g** are efficient antiproliferative medicines on hormone-dependent contrary to the independent human breast cancer.

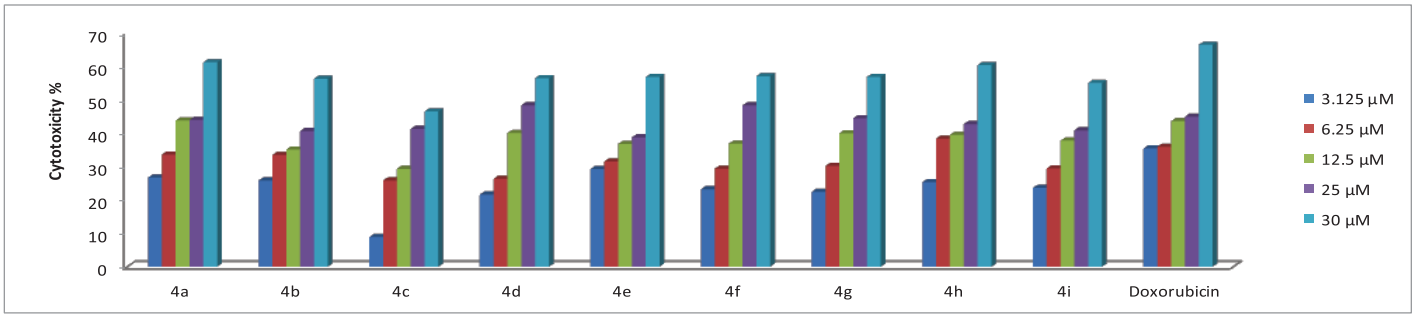


Figure 3. Dose-dependent antiproliferative effects of **4a–4i** compounds on HCT-116 cancer cells via the MTT assay.

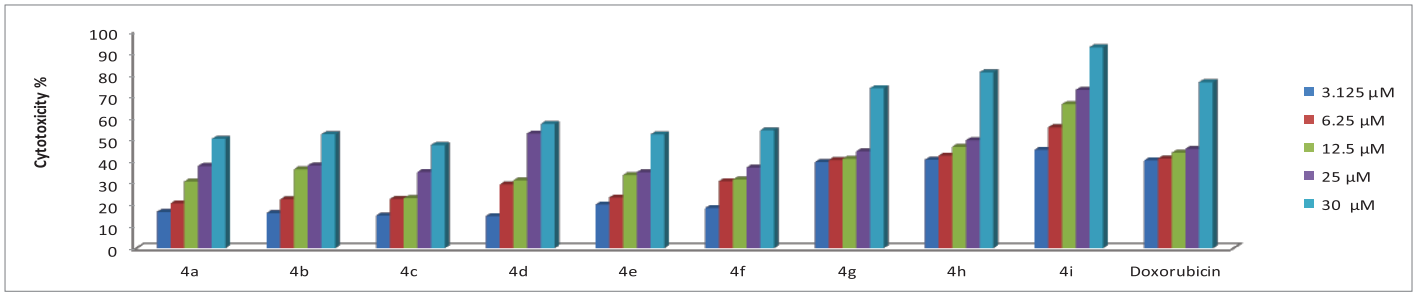


Figure 4. Dose-dependent antiproliferative effects of **4a-4i** compounds on MCF-7 cancer cells via the MTT assay.

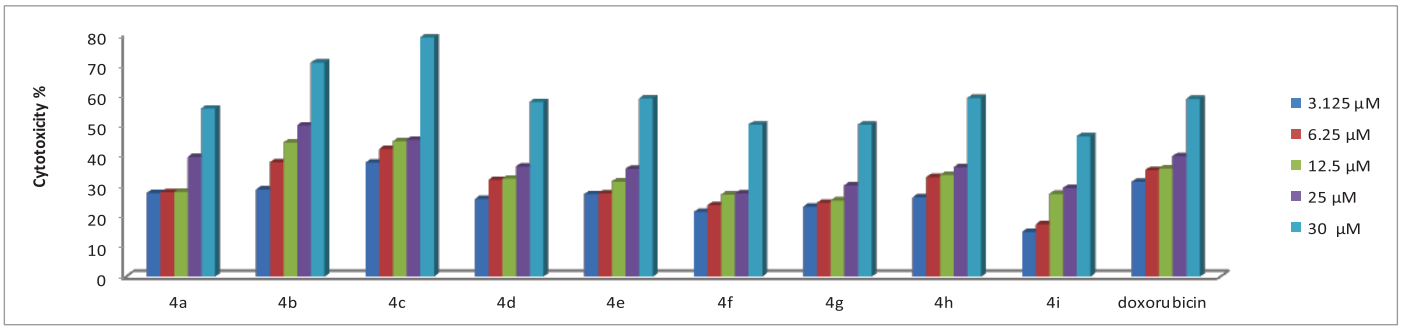


Figure 5. Dose-dependent antiproliferative effects of **4a–4i** compounds on MDA-MB-231 cancer cells via the MTT assay.

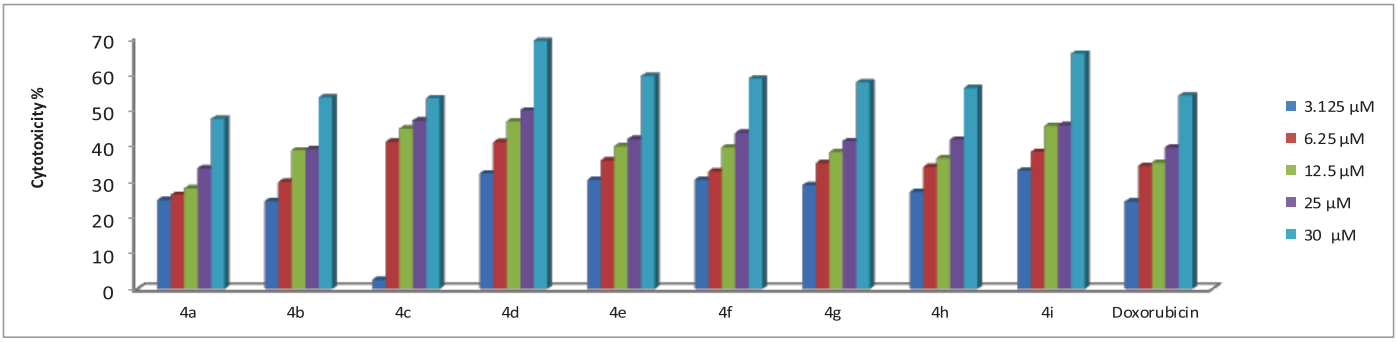


Figure 6. Dose-dependent antiproliferative effects of **4a–4i** compounds on A549 cancer cells via the MTT assay.

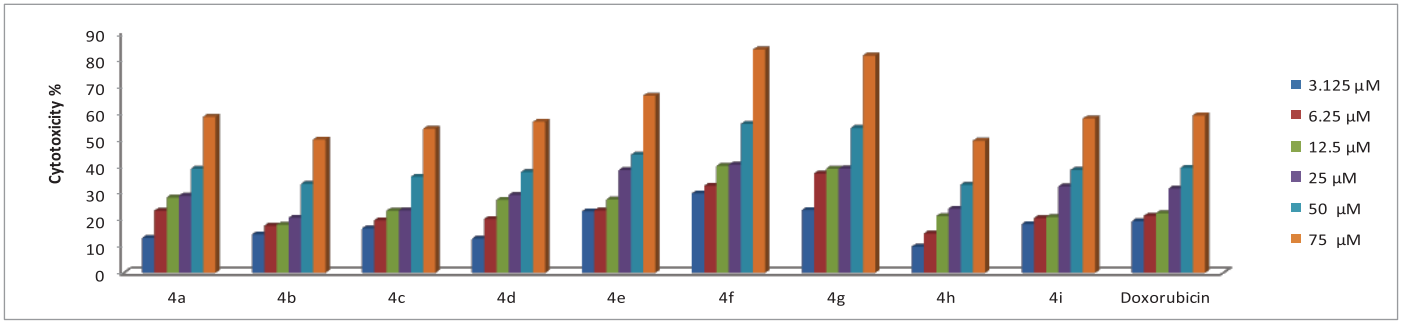


Figure 7. Dose-dependent toxic effects of **4a**–**4i** compounds on RPE-1 human normal cells via the MTT assay.

Table 3. TI of the compounds' activities on the four cancer types relative to the normal cells according to the results in Table 2.

Compounds	TI = ED_{50}/TD_{50}			
	HCT-116	**MCF-7**	**MDA-MB-231**	**A549**
4a	2.6	2.1	2.4	2.0
4b	2.8	2.6	3.6	2.7
4c	2.2	2.2	3.8	2.5
4d	2.5	2.5	2.6	3.1
4e	2.2	2.0	2.2	2.2
4f	1.7	1.6	1.5	1.8
4g	1.8	2.3	1.5	1.8
4h	3.1	4.1	3.0	2.8
4i	2.4	6.1	2.0	2.8
Doxorubicin	2.8	3.3	2.5	2.3

Table 2. EC_{50} of the compounds on the four human cancer types and the TD_{50} on the noncancerous human normal cells via the MTT assay.

Compounds	ED_{50} (µM) ± SD				TD_{50} (µM) ± SD
	HCT-116	**MCF-7**	**MDA-MB-231**	**A549**	**RPE-1**
4a	24.5 ± 3.3	29.8 ± 4.5	27.0 ± 4.1	31.7 ± 4.5	64.5 ± 5.1
4b	26.7 ± 3.9	28.6 ± 4.2	21.3 ± 3.7	28.2 ± 4.2	75.5 ± 5.5
4c	32.3 ± 4.2	31.6 ± 4.9	18.3 ± 3.5	28.3 ± 4.1	69.8 ± 4.9
4d	26.6 ± 3.8	26.3 ± 3.9	26.0 ± 3.5	21.8 ± 3.4	66.6 ± 5.3
4e	26.4 ± 3.9	28.6 ± 3.9	25.5 ± 4.2	25.3 ± 3.8	56.8 ± 4.5
4f	26.3 ± 3.8	27.7 ± 4.2	29.9 ± 4.9	25.6 ± 3.9	45.1 ± 4.2
4g	26.4 ± 4.1	20.4 ± 2.9	29.9 ± 4.7	26.1 ± 3.9	46.3 ± 4.1
4h	24.9 ± 3.9	18.5 ± 2.3	25.5 ± 3.7	26.9 ± 4.1	76.2 ± 5.9
4i	27.3 ± 3.9	10.6 ± 1.8	32.4 ± 4.9	22.9 ± 3.1	65.5.2
Doxorubicin	22.6 ± 3.6	19.6 ± 2.9	25.5 ± 3.1	27.9 ± 4.1	63.9 ± 4.3

The therapeutic index (TI) of the compounds, which was calculated by dividing their efficacious dose for 50% of the cancerous cells population (ED_{50}) over their toxic dose in 50% of the noncancerous cells population, is presented in Table 3 (Hatem *et al*., 2019). From Table 3, it is obtained that the TI ranged from 1.7 to 3.1 compared to 2.8 for the reference drug on human colon cancer. In addition, TI ranged from 1.6 to 6.1 relative to 3.3 for the reference drug on the hormone-dependent human breast adenocarcinoma. While the TI ranged from 1.5 to 3.8 relative to 2.5 for the reference drug on the hormone-independent human breast adenocarcinoma. In addition, TI ranged from 1.8 to 3.1 relative to 2.3 for human lung cancer reference drugs. These results indicate that all synthetic compounds have the same efficacy and safety, or better in some compounds, than the standard drug doxorubicin.

Structure activity relationships discussion

In general, triazolopyrimidine derivatives have a function of promoting biological activity. In this work, all

synthetic compounds have a built-in triazolopyrimidine unit with an important indole moiety at the 5-site. The compound **4a** with 4-chlorophenyl at 7-position has the greatest antiproliferative activity against HCT-116 (EC_{50} = 24.5 μM), followed by compound **4h** (EC_{50} = 24.9), which comprises a pyrrole unit at 7-site. While with MCF-7 cells, **4i** (EC_{50} = 10.6 μM), which contains the bi-indole rings, compound **4h** (EC_{50} = 18.5 μM), which contains a pyrrole ring at 7-position, and compound **4g** (EC_{50} = 20.4 μM), which has a furan ring at 7-site are anticancer applicants on hormone-dependent instead of on hormone-independent human breast cancer. For, MDA-MB-231, compound **4c** (EC_{50} = 18.3 μM), which was substituted with 4-bromophenyl at position 7, and compound **4b** (EC_{50} = 21.3 μM), which was substituted with 4-nitrophenyl at position 7, had more effect; compound **4h** (EC_{50} = 25.5 μM), with pyrrole unit at the 7-site, and compound **4e** (EC_{50} = 25.5 μM), substituted with 2-nitrophenyl at 7-position, had equipotent effects; compared to doxorubicin, compound **4i** (EC_{50} = 32.4 μM), with the bi-indole rings, had a significantly lesser antiproliferative effect. In the A549 cancer type, compound **4d** (EC_{50} = 21.8 μM), substituted with 2-nitrophenyl at 7-position, had more antiproliferative activity; compared to doxorubicin, compound **4a** (EC_{50} = 31.7 μM), substituted with 4-chlorophenyl at 7-position, had insignificantly lesser antiproliferative effects. Moreover, these results indicate that all synthetic compounds have the same efficacy and safety, or better in some compounds, than the standard drug doxorubicin.

CONCLUSION

The conventional three-component reactions have been used to construct a new series of triazolopyrimidine derivatives with built-in indole moiety. Compared to other traditional methods, this method is advanced in its cost-effectiveness, is easy to set-up, and results in high product quality. Antiproliferative activity of the new compounds has been examined toward four different human cancer cells and one human healthy cell line. Compounds **4a** and **4h** are active against the human colon cancer; all triazolopyrimidines are active toward MCF-7; **4i**, **4h**, and **4g** are effective anticancer applicants on hormone-dependent instead of hormone-independent MCF-7. Consequently, it was found that the triazolopyrimidine derivatives could be studied for further biological investigation. Moreover, the multicomponent method is promising in the synthesis of many additional heterocyclic compounds.

ACKNOWLEDGMENTS

We express our appreciation to the National Research Centre and Qassim University for the services provided.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FINANCIAL SUPPORT AND SPONSORSHIP

None.

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How to cite this article:
Radwan M, Alminderej F, Tolan H, Awad H. One-pot three-component synthesis of new triazolopyrimidine derivatives bearing indole moiety as antiproliferative agents. J Appl Pharm Sci, 2020; 10(09):012–022.