One-Pot Synthesis Compounds of 1,2,3-Triazole, and Triazoline and Studying Its Biological Efficacy Against Colon Cancer

Nabeel A. Abdul-Rida[1], Arkan H. Jawad[2]
[1, 2]Department of Chemistry, College of Education, University of Al-Qadisiyah, Iraq.
Email: ahj1977ahj@gmail.com

Abstract
A series of novel 1,2,3-triazole, 1,2,3-triazoline compounds was synthesized via 1,3-dipolar cycloaddition with high yield in a short duration. All the compounds were characterized by using FT-IR and NMR spectroscopic techniques. The compound was selected 2-(4-(1-benzyl-1H-1,2,3-triazol-4-yl) butyl) isoindoline1,3-dione and its effectiveness against colon cancer cells was studied and it gave good inhibition results.

1. Introduction

Heterocyclic compounds are cyclic organic compounds that contain at least one heteroatom; the most common heteroatoms are nitrogen, oxygen, and sulphur, but heterocyclic rings with additional heteroatoms are also well-known. A carbocyclic compound is a cyclic organic compound with all carbon atoms arranged in a ring. Heterocyclic compounds are one of the most important types of organic chemicals. Because of its action in a variety of disorders, it is used in a variety of biological domains. DNA and RNA, for example, are biological molecules (1-3).
The heterocyclic ring is found in the primary skeleton of chlorophyll, haemoglobin, vitamins, and many other compounds. Heterocyclic compounds are plentiful. Triazine derivatives have been utilized as antibacterial herbicides and urinary antiseptics in the treatment of a variety of ailments, as well as anti-inflammatories Benzimidazole (4-6).
Phthalimides have a structure (-CO-N(R)-CO-) and due to the presence of an imide group in their composition helped them to be biologically active, so phthalimides received attention by researchers as they showed an important role in drug discovery (7,8), It has many biological properties such as anticancer (9), antioxidant (10), antimicrobial (11) and anti-inflammatory (12,13).
Triazoles and Triazoline they are heterogeneous pentagonal rings, containing two carbon atoms and three nitrogen atoms, with the molecular formula C2H3N3 , There is wide interest in triazole derivatives because of their wide applications in medicine, agriculture, materials science and industrial chemistry, due to their unique structure and properties. Cancer (14), anti-tuberculosis (15), antihypertensive (16), and antidepressant (17).
The coupling of two or more steps in one reaction vessel represents a process aimed at higher production, fewer steps, higher purification and lower energy consumption, and therefore this type of reaction is compatible with the concepts of green chemistry (18).
Therefore, the one-pot reaction process is considered an economical method, and it is by intensifying a number of steps to build bonds, which includes the creation of new compounds (intermediate and final) without isolating intermediate compounds. In the recent period, there have been attempts to obtain highly selective chemical compounds at a lower economic cost and with a good final product. Therefore, the use and development of methods for one-step reactions has increased, and one of the most important methods used to achieve this is the multi-component reaction (MCR), where three primary materials interact or more in one reaction vessel to prepare a product that contains parts of all components, which is the opposite of a gradual reaction that requires preparing the intermediate material, isolating it, and then creating a new reaction, and these chain reactions include two or more steps of bond formation that occur in the same reaction conditions In a sequential manner, where the reactions that are prepared can meet the desired goals and with high efficiency without the need to purify the intermediate compounds and significantly reduce the waste of materials and time and increase the amount of products (19).
Click chemistry has gained great importance and found its applications in all aspects of research and technology that use organic molecules such as polymer science (20) and nanoscience (21), photochemistry (22), bioconjugation and sensor development (23,24).
The reaction of (CuAAC) catalysed with Cu(I) has a gradual mechanical process that includes copper in the first step where it forms acetyl copper by coordination with an alkene, in the second step the azide bonds with copper followed by the formation of an unconventional metal cycle of Cu(II). The media then undergoes ring contraction to give the copper a triazole derivative, which upon proton decomposition gives the desired 1,2,3-Triazole product (25,26).

2. 2. Experimental

2.1Materials and methods

FTIRSpectra was done in the range of (4000-400 cm-1 by using KBrdisk which were

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recorded on a SHIMADZU FTIR-8400S fourier.transform.proton nuclear magnetic resonance were recorded on fourier transformation bruker spectrometer ,operating at (500MHz) with (DMSO-d6) measurments were made at Department of chemistry , university of Tehran in Iran. Elemental analysis measured on EAS superuser elemental analyser system GmbH, access: VarioELsuperuser [1].

2.2. Chemical synthesis

2.2.1. synthesis of 2-(1,3-dioxoisoindolin-2-yl) ethyl 4-methylbenzenesulfonate (3)

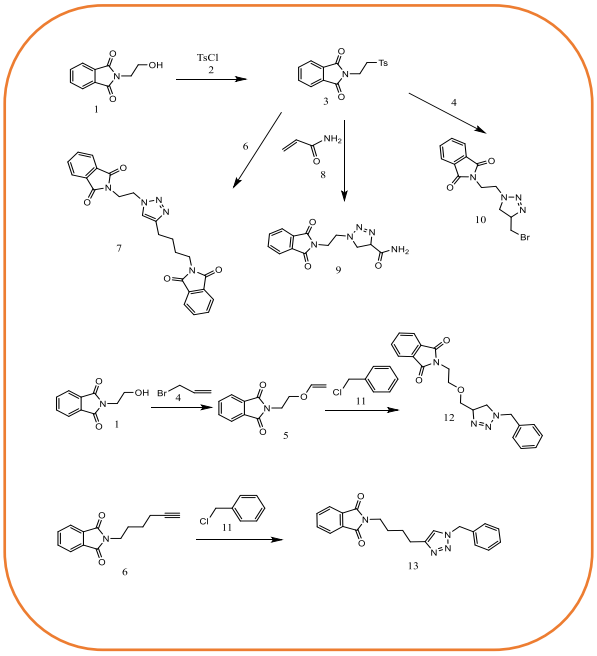
In a 250 mL two-hole flask, 4-toluene sulfonyl chloride (9.8 mmol, 1.9 gm) was dissolved in (10 mL) pyridine and added to a solution consisting of 2-(2-hydroxyethyl)isoiandoline-1-3-dione (8.9 mmol , 1.70gm) dissolved in (24ml) of CH2Cl2 at 0Cº, the mixture was left to rise to its temperature quietly to room temperature, then the mixture was stirred for 24 hours and followed up by TLC:(benzene: methanol)(4:1) (V:V) After the reaction is finished, a saturated solution of sodium bicarbonate NaHCO3 (10ml) is added to the mixture, and then the organic layer is separated from the aqueous layer by adding (2×20ml) CH2Cl2, the organic layer is dried by adding anhydrous magnesium sulphate MgSO4 and then filtered. The solvent is removed by distillation under vacuum pressure to obtain a white precipitate after recrystallization with absolute ethanol. to yield 3 (2.70gm, 75%) white crystals [2].

2.2.2. Synthesis of 2-(2-(allyloxy) ethyl) isoindoline-1,3-dione (5)

2-Phthalimdoethanol (10mmol, 1.91gm) dissolved in (25 ml) acetone dry taken in round bottom flask with add potassium carbonate (15mmol ,1.67gm) Stirrer the mixture for (15minute), then add allyl bromide (10mmol,1.2ml) slowly added in a round bottom flask, then stirrer the mixture to (24 h) at a temperature (50 C°), The progress of the reaction was monitored by TLC. After the completion of the reaction, cool the mixture, then pour it over the ice water and then the organic layer was separated from the aqueous layer using a separating funnel by (3×15) Chloroform, then dried by ($MgSO_4$) and filter, the solvent was removed under vacuum, it was completed Obtaining a white precipitate after recrystallizing with absolute ethanol.

2.2.4. General Procedure to synthesis compound (9,11,12,14,15)

Dissolved (3,11) (3.36mmol/1.68mmol) in mixture from (DMF:H2O) in the rate of (1:1) in the round flask bottom (100ml) , then added to it (1.68mmol/3.36mmol) from sodium azide dissolved in (2.5-5 ml) distilled water , leave the reaction for half an hour , then added (1.68mmol/3.36mmol) from (4,5,6,8) dissolved in (8-15ml) DMF , then added (CuSO4.5H2O) (0.085-0.170mmol) and sodium ascorbate (0.170-0.34mmol) Dissolved in a small amount of distilled water , Stirrer the mixture for (48-72h) at a temperature (60Cº) , the progress of the reaction was monitored by TLC , After the completion of the reaction mixture is cooled with ice water and then the organic layer were separated from the aqueous layer using a separating funnel by (3×15) Chloroform , then dried by(MgSO4) and filter , the solvent was removed under vacuum, it was completed Obtaining a white precipitate after recrystallizing with absolute ethanol.



Scheme 1. Preparation of Compounds (3-13)

3. 3. Results and Discussion

3.1 The compound (3) 2-(1,3-dioxoisoindolin-2-yl) ethyl 4-methylbenzenesulfonate is white crystals yield 75% M.P 139 Cº

The infrared spectrum of compound (3) showed band at (1426,1463cm-1) for (C=C) aromatic, (1603cm-1) for (Ts), (1712cm-1) for (C=O), (2950cm-1) for (C-H) aliphatic, (3061cm-1) for (C-H) aromatic.

The 1H-NMR (DMSO-d6) spectrum data of compound (3) show: 3.32 (s, Ar-CH3) ,3.78 (t, H-2, N-CH2), 4.27 (t, H-3, O-CH2), 7.14-7.85 (m, H-4,5,6, Ar-H).

The 13C-NMR (DMSO-d6) spectrum data of compound (3) show: 22.34 (C-1,Ar-CH3) , 37.90 (C-2,N-CH2) , 68.72 (C-3,O-CH2) , 124.33-146.12 (C-4,5,6,7) , 168.61 (C=O).

3.2 The compound (5)2-(2-(allyloxy) ethyl) isoindoline-1,3-dione is white crystals yield 85%, P.M 125Cº.

The infrared spectrum of compound (5) showed band at (1057cm-1) for (C-O-C) , (1541,1558cm-1) for (C=C) Aromatic , (1697cm-1) for (C=C) aliphatic , (1768cm-1) for (C=O) , (2983cm-1) for (C-H) aliphatic , (3066cm-1) for (C-H) Aromatic , (3097cm-1) for (C-H) double bond.

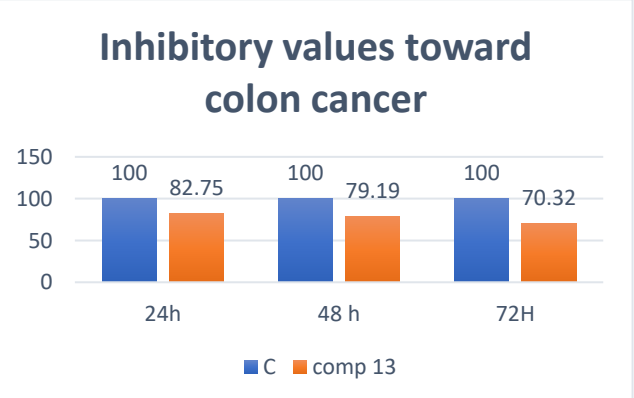
The 1H-NMR (DMSO-d6) spectrum data of compound (5) show: 2.53 (t, H-1, O-CH2) , 2.98(t,H-2,N-CH2) , 3.21 (d,H-3,O-CH2-C=), 3.46(d,H-4),5.04(m,H-5), 7.19-7.51 (m,H-6,7,Ar-H).

3.3 The compound (7) 2-(2-(4-(4-(1,3-dioxoisoindolin-2-yl) butyl)-1H-1,2,3-triazol-1-yl) ethyl) isoindoline-1,3-dione is

yellow powder yield 68%, P.M154Cº.
The infrared spectrum of compound (7) showed band at (1427,1462cm-1) for (C=C) aromatic, (1592cm-1) for (C=C) aliphatic, (1705cm-1) for (C=O), (2935cm-1) for (C-H) aliphatic.
The 1H-NMR (DMSO-d6) spectrum data of compound (7) show :1.04(m, H-1), 1.59(m, H-2) ,2.61(t, H-3, CH2),3.41(t, H-4, N-CH2),3.57(t, H-5, Ar-CH2), 5.51(t, H-6),7.24-7.86(m,Ar-H).
The 13C-NMR (DMSO-d6) spectrum data of compound (7) show: 24.97(C-1), 26.72(C-2),37.59(C-3),40.28(C-4,N-C),53.06(C-5), 123.54(C-6,C=C), 136.74(C-7),128.47-147.29(C-7,8,9,10,11,12. Ar-C),168.41(C-13,C=O).
3.4 The compound (9) 1-(2-(1,3-dioxoisoindolin-2-yl) ethyl)-4,5-
dihydro-1H-1,2,3-triazole-4-carboxamide is white crystals yield 75%, P.M. 132Cº
The infrared spectrum of compound (9) showed band at (1462,1531cm-1) for (C=C) aromatic, (1705cm-1) for (C=O), (3005cm-1) for (C-H) Aromatic, (3464cm-1) for (N-H).
The 1H-NMR (DMSO-d6) spectrum data of compound (9) show :2.21(t, H-1),3.32(d,H-2,N-CH2),3.79(t,H-3,N-CH2),4.27(t,H-4.N-CH2), 5.39(s,H-5,N-H), 7.17-7.84(m,H-6,7,Ar-H).
3.5 The compound (10) 2-(2-(4-(bromomethyl)-4,5-dihydro-1H-1,2,3-
triazol-1-yl) ethyl) isoindoline-1,3-dione is green powder light yield 70%, P.M 138Cº.
The infrared spectrum of compound (10) showed band at (1462,1593cm-1) for (C=C) aromatic, (1708cm-1) for (C=O), (659cm-1) for (C-Br).
The 1H-NMR (DMSO-d6) spectrum data of compound (10) show :2.21(d, H-1) ,2.27(t, H-2, N-CH2),3.79(d, H-3, Br-CH2),4.27(t, H-4, N-CH2),7.16(t, H-5, N-CH),7,55-7.86(m, H-6,7, Ar-H).
The 13C-NMR (DMSO-d6) spectrum data of compound (10) show :21.52(C-1, Br-C) ,37.09(C-2, N-C),39.69(C-3, N-C),40.36(C-4, N-C),67.90(C-5),123.52-145.31 (C-6,7,8,Aromatic),167.80(C-9,C=O).
3.6 The compound (12) 2-(2-((1-benzyl-4,5-dihydro-1H-1,2,3-triazol-4-
yl) methoxy) ethyl) isoindoline-1,3-dione is brown liquid yield 65%.
The infrared spectrum of compound (12) showed band at (1023cm-1) for (C-O), (1404-1436cm-1) for (C=C) aromatic, (1711cm-1) for (C=O), (2917cm-1) for (C-H) aliphatic, (3005cm-1) for (C-H) aromatic.
The 1H-NMR (DMSO-d6) spectrum data of compound (12) show : 2.39(d,H-1,N-CH2) ,2.66(d,H-2,O-CH2), 2.99 (t,H-3,O-CH2),3.63(t,H-4,N-CH2),3.95(t,H-5,N-CH),4.49(s,H-6,N-CH2),7.20-7.82(m,H-7,8,9,10,Ar-H).
The compound (13) 2-(4-(1-benzyl-1H-1,2,3-triazol-4-yl) butyl) isoindoline-
1,3-dione is brown powder yield 64%, P.M 164.
The infrared spectrum of compound (13) showed band at (1516,1530cm-1) for (C=C) aromatic, (1701cm-1) for (C=O), (2939cm-1) for (C-H) aliphatic, (3055cm-1) for (C-H) aromatic, (3097cm-1) for (C-H) for double bond.
The 1H-NMR (DMSO-d6) spectrum data of compound (13) show :1.04(m, H-1) ,1.59(m, H-2),2.61(t,H-3),3.41(t,H-4,N-CH2),3.57(s,H-5,N-CH2),5.51(s,H-6),7.24-7.86(m,H-7,8,9,10,Ar-H).
The 13C-NMR (DMSO-d6) spectrum data of compound (13) show :24.97(C-1), 26.27(C-2), 37.59(C-3),40.28(C-4),53.06(C-5),123.45(C-6),136.74(C-7),128.21-147.29(C-Ar),168.41(C=O).

4. 4. Study of the anticancer activity

The compound [13] was selected to study its antifungal activity for cancer, for colon cancer, where this study included two lines of infected cancer cells and to know the ability of the compound [13] and its pharmacological efficacy to kill cancer cells. The compounds were prepared with different concentrations (6.25,12.5,25,50,100 mM micro), and the effect was studied Compound for this type of cancer.
The effectiveness of the compound [13] against colon cancer cells HCT116 was studied multiple concentrations (6.25,12.5,25,50,100 µg/ml of the compound were used) [13] If the culture medium (Medium) was used to activate cancer cells at a temperature the process of culturing these cells (1×104 cells/ml) was carried out in flat plates containing (5%) and 37Cº (96-Well-Flat-bottom-culture Plates) (96-well-flat-bottom-culture plates) of carbon dioxide and placed in the incubator for (48) hours, after which cells were treated nano chrysin and at concentrations of (6.25,12.5,25,50,100 µg/ml) for a period of (24) an hour after that, dye (MTT) is added at a rate of 100 microliters per hole, and then we put it in incubate for 4 hours, then isopropanol was added at a rate of (100 µl) per hole using a micro-ELISA reader, and the optical efficiency was measured at a wavelength of 450 nm (27)[3].
The compound [13] was investigated as an anti-colon cancer using a cell line HCT116, where the biological results examined by the MTT method showed for the base material and derivatives, where (Scheme 2) shows the percentage of inhibition at the concentration (100 µg.ml-1) at (24,48,72h), where it turns out that the highest percentage of inhibition of cancer cells is (82.75%) at (24h)(28,29)[4].

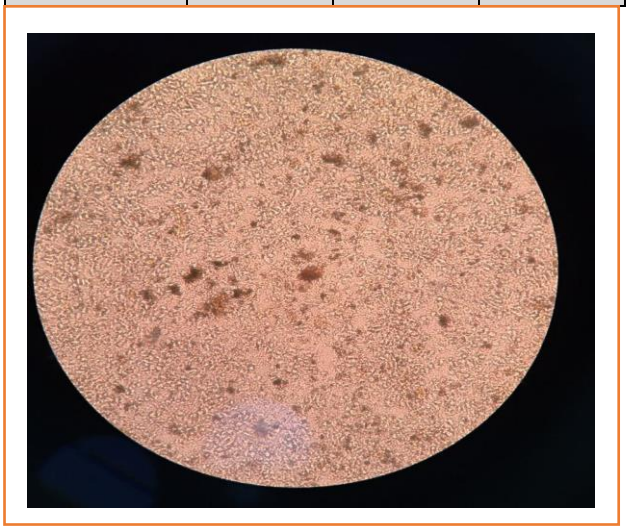


Scheme 2 Inhibitory values toward colon cancer

Also, the cytotoxicity IC_{50} µg/ml of the compound was measured at different time intervals (24,48,72

hours), the results were as in the table 1.

Table 1 shows the IC50 cytotoxicity values for the compound [13]			
Comp	24h	48h	72h
13	17.25	20.81	29.68



The figure1: shows the effect of the compound [13] on colon cancer

5. 5. Conclusions

Simple and rapid synthesis was carried out from one container of several compounds 3,2,1-triazole and triazoline and through the process of 3,1-dipolar cycloaddition, the compounds were validated by infrared spectroscopy, 1H-NMR and 13C -NMR, then the biological activity and degree of inhibition of colon cancer cells were studied for one of the prepared compounds, which is [13] where it showed good activity. The biological activity can be applied to the prepared compounds and studied further.

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