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ULTRASONICALLY ASSISTED SYNTHESIS OF CHROMEN-2-ONE-1,2,3-TRIAZOLES AND *In-vitro* ANTICANCER ACTIVITY

Jagadeesh Kumar Ega[1,✉], Prashanth Raja Peddapyata[1] and Kavitha Siddoju[2]
Department of Chemistry, Chaitanya (Deemed to be University), Hanamkonda, Telangana-506001
✉Corresponding Author: jkjagadeeshkumare@gmail.com

ABSTRACT
Synthesis of new series of chromen-2-one-1,2,3-Triazoles (6a-6j) was reported using the help of key methods such as [3+2]-cycloaddition and ultrasound. All compounds were further evaluated for their *in vitro* anticancer activity profile in three human cancer cell lines MCF-7(breast), A-549 (lungs), and HeLa (cervical). Among all, three compounds namely 6c, 6f, and 6j showed the most promising activity against three lines, when compared with the etoposide.
Keywords: Chromen-2-One, 1,2,3-Triazoles, Huisgen Cycloaddition, Ultrasonication
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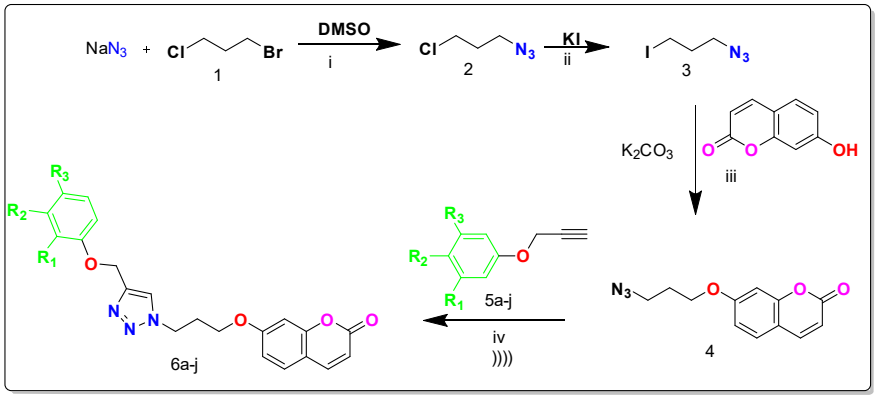
INTRODUCTION

Triazole is an efficient class of N- based heterocycles and found to be an attractive entity to the medicinal research community[1] since it can form *H*- holding, which can supreme preventive target.[2-3] These portions show diverse natal applications like anti-HIV,[4] antimicrobial[5-7] and anticancer, etc., Cu (I) - accelerated addition of azides and terminal alkynes,[8-10] an obliging method. Cefatrizine (4), and Carboxyamidotriazole[5] (Fig.-1) are under clinical trials for cancer therapy. Accordingly, the 1,2,3-triazole would be utilized as a key unit in the construction of novel anti-cancer compounds. Remarkably, several chromen-2-one-based compounds as potent anticancer agents were available in the literature.[16] CXL017 (1), CXL035 (2) & CXL055 (3), are used for the treatment of different cancers (Fig.-2). Outstandingly, the ultrasound light could come with the obvious response yield with prolonged rates as well as a diminished immediate response.[11-15] Ultrasonic-helped natural union is an incredible method that is being utilized increasingly to speed up the natural response rate. Based on all the above concepts, herein, we discussed the alteration of the 1,2,3-*T*riazole component intense on chromen-2-one utilizing the Ultrasonic method.



6a: $R_{1=}$ H, $R_{2=}$ H, $R_{3=}$ H, Yield (%) 90; 6b: $R_{1=}$ NO_2, $R_{2=}$ H, $R_{3=}$ H, Yield (%) 89;
6c: $R_{1=}$ H, $R_{2=}$ H, $R_{3=}$ NO_2, Yield (%) 91; 6d: $R_{1=}$ OCH_3, $R_{2=}$ H, $R_{3=}$ H, Yield (%) 91;
6e: $R_{1=}$ H, $R_{2=}$ OCH_3, $R_{3=}$ H, Yield (%) 93; 6f: $R_{1=}$ H, $R_{2=}$ H, $R_{3=}$ OCH_3, Yield (%) 90;
6g: $R_{1=}$ CH_3, $R_{2=}$ H, $R_{3=}$ H, Yield (%) 88; 6h: $R_{1=}$ H, $R_{2=}$ CH_3, $R_{3=}$ H, Yield (%) 94;
6i: $R_{1=}$ H, $R_{2=}$ CH_3, $R_{3=}$ Cl, Yield (%) 86; 6j: $R_{1=}$ Cl, $R_{2=}$ CH_3, $R_{3=}$ Cl, Yield (%) 82.

Scheme-1: Route of the Title Compounds (6a-6j)

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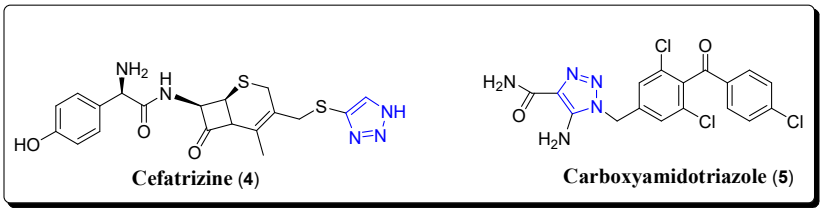

Fig.-1: 1,2,3-Triazole Based Molecules Underneath Clinical Trial for Cancer Therapy

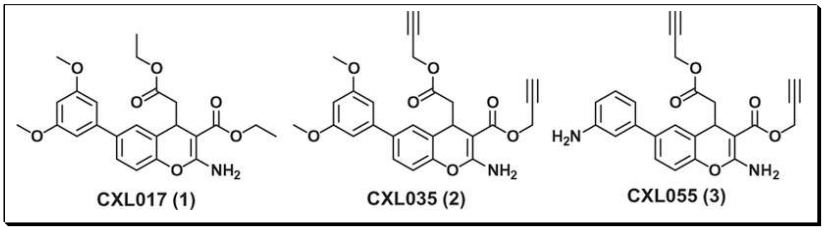

Fig.-2: Various Chrome-2-One Drugs as Cancer Drugs

The hybrid molecules made of two or more different pharmacophore units have the potential to minimize side effects and they can overcome drug resistance.

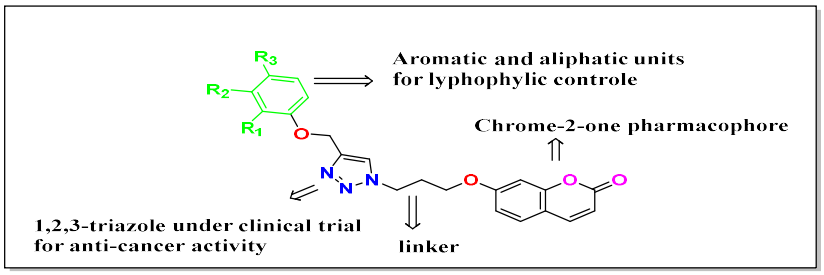

Fig.-3: Hybridization Strategy for Merging of Two Pharmacophores

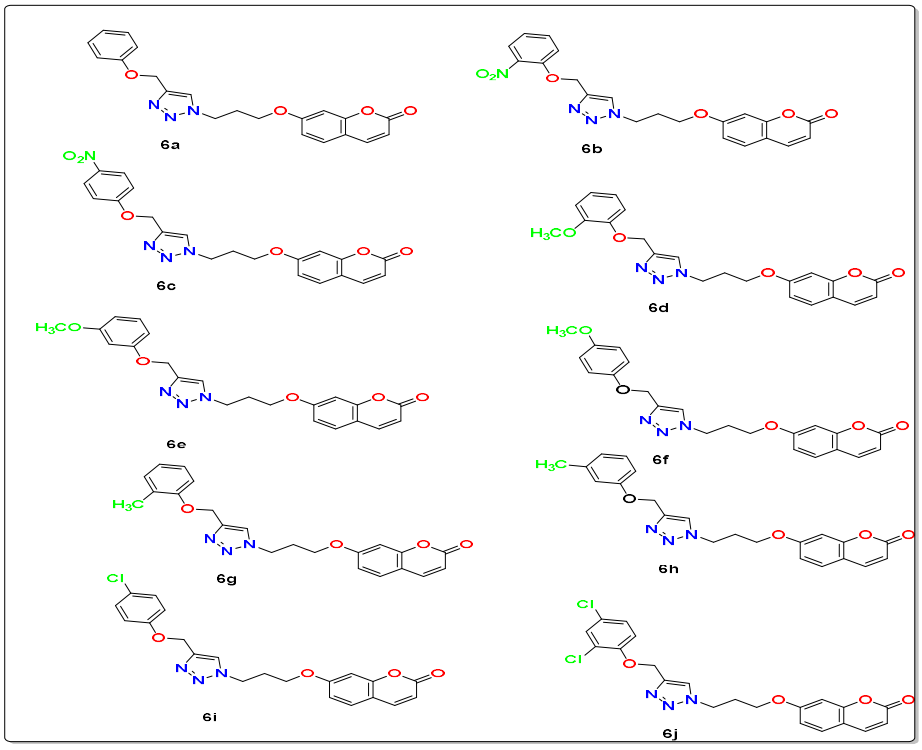

Fig.-4: Structures of Entitled Compounds 6a-6j

EXPERIMENTAL

Material and Methods

TLC was performed by using Merck silica gel 60F254 precoated plates (0.25 mm) and column chromatography was performed by using Silica gel (particle size 100-200 mesh). Proton nuclear Magnetic Resonance (400 MHz) and Carbon Nuclear Magnetic Resonance (100 MHz) spectrums were logged on Bruker AC-300 spectrophotometer in $CDCl_3$ with *TMS* as reference. The mass spectrum was documented on the JEOL SX-102 spectrophotometer. All the chemicals and reagents used in the present investigation were purchased from Sigma Aldrich Chemical Company. Digital ultrasonic cleaner 120 W FREQ 40KHz of 2L tank size 150 ×135×100 mm of model PS-10.

General Procedure for the Synthesis of 1,2,3-triazol-1-yl)propoxy)-2*H*-chromen-2-one (6a)

1-Bromo-3-chloropropane (1) (10 mmol) is treated with NaN_3 by using DMSO solvent for 2-3 h to obtain 1-azido-3-chloropropane (2). It is furthermore treated with KI at RT for h to produce 1-azido-3-iodopropane (3). To an RB containing 1-azido-3-iodopropane (3) (10 mmol) in dry DMF, 24 mmol of K_2CO_3 was added part shrewd up to 15 minutes, and the 10 mmol of 7-hydroxy-2H-chromen-2-one (iii) added and the consequent combination was animated at RT for 4hs and removed 2 times with 10 ml of EAA and water to yield 7-(3-azidopropoxy)-2*H*-chromen-2-one (4). Finally, a mixture of the terminal alkyne (5a), aryl azide, and copper sulfate/sodium ascorbate in DMSO/H_2O was stirred under ultrasonication at 120 W FREQ 40 KHz for 30 min. The crude product was separated via filtration and then purified by 60-120 mesh size column chromatography using a mixture of equal volumes of hexane/ethyl acetate as an eluent gradient to get the anticipated product 6a.

RESULTS AND DISCUSSION

Chemistry

Authors illustrated the edifice of novel 1,2,3-triazol-1-yl)propoxy)-2*H*-chromen-2-one as presented in Scheme 1. 15 mmol of 1-(prop-2-ynyloxy) benzene (5a) and 20 mmol aryl azide added Sharpless catalyst, DMSO/H_2O (9;1), and mixture is ultrasonication 120 W FREQ 40KHz for 30 min stirring to give promising yield (6a) via 1,3-dipolar addition reaction(6a-j) yields are (86%–94%). Alkali azide was first reacted with 1-Bromo-3-chloropropane (1) at RT to outline 1-azido-3-chloropropane (2) in DMSO. Next, the reaction between intermediate 2 with KI gives the 1-azido-3-iodiopropane intermediate (3). To intermediate 3, the Chromen-2-one group was added using K_2CO_3 to give the intermediate 7-(3-azidopropoxy)-2*H*-chromen-2-one (4). (86%–94%). The following transformations are involved 4 steps. In step i azide formation from 1 to 2, halogen substitution from 2 to 3in step ii, O- alkylation from step iii, and cycloaddition in between terminal alkynes 5a-j with azide 4 catalyzed by in situ cuprous catalyst to give compounds 6a-j.

In-vitro Anticancer Activity

Compounds (6a– 6j) were further investigated for in vitro anticancer activity towards three cell lines, including MCF-7, A-549, and HeLa with the help of MTT assay using the etoposide was +ve direct and the results were shown in Table-1. Among all, three compounds 6c, 6f, and 6j compound were shown to have the most promising activity against all three cell lines as compared to the etoposide. In detail, compound 6j was shown the most potent activity against (IC_{50} = 3.82± 0.96, 4.82 ± 0.33, and 9.12 ± 0.96 μM for MCF-7, A-549, and HeLa cell lines respectively. The next better activity was shown by the compound 6f (IC_{50} = 5.04 ± 1.39, 5.84 ± 0.44, and 11.18 ± 2.94 μM) for MCF-7, A-549 HeLa cell lines respectively. The compound 6c was ranked 3rd in this order which showed (IC_{50} = 6.04 ± 1.46, 6.92 ± 0.52, and 13.14 ± 5.04μM for MCF-7, A-549 HeLa cell lines. The respite of compounds is good to nil potency on selected cell lines as compared to the positive control.

Table-1: *In vitro* Cytotoxic Activity of Compounds (6 a– 6 j) in (IC50 μM)

Entry	R	MCF-7 [b]	HeLa [c]	A-549 [d]
6a	C_6H_5	24.14± 6.27	23.65 ± 8.64	ND
6b	2-$NO_2C_6H_4$	ND	13.48 ± 4.84	16.26 ± 5.62

6 c-3	4-$NO_2C_6H_4$	6.04 ± 1.46	6.92 ± 0.52	13.14 ± 5.04
6 d	2-$OCH_3C_6H_4$	10.09 ± 3.04	11.78 ± 1.08	16.26 ± 6.62
6 e	3-$OCH_3C_6H_4$	11.52± 2.32	14.12 ± 2.14	18.41 ± 7.44
6 f-2	4-$OCH_3C_6H_4$	5.04 ± 1.39	5.84 ± 0.44	11.18 ± 2.94
6 g	2-$CH_3C_6H_4$	18.31 ± 2.82	ND	29.23 ± 3.42
6 h	3-$CH_3C_6H_4$	18.06 ± 2.79	16.84 ±1.42	27.18 ± 3.21
6 i	4-ClC_6H_4	4.15 ± 1.02	6.43 ± 1.67	10.74 ± 1.88
6 j-1	2,4-diClC_6H_3	3.82± 0.96	4.82 ± 0.33	9.12 ± 0.96
Etoposide		3.08 ± 0.21	2.31±0.14	6.14±0.47

[a] Mean ±S. D values from three different experiments performed 9.12 ± 0.96in triplicates.
[b] MCF-7: Breast cancer cell line.
[c] HeLa: Cervical cancer cell line.
[d] A549: Lung cancer cell line.

^{1}H NMR (400MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$) and LCMS Data of the Title Compounds (6a-6j)

6a: Yield (90%); *δ* 7.94 – 7.47 (m, 3H), 7.38 – 7.05 (m, 3H), 7.02 – 6.65 (m, 4H), 6.42 (d, 1H), 5.14 (s, 2H), 4.45 – 3.44 (m, 4H), 2.17 (dd, 2H). δ 162.26, 159.22, 156.24, 143.07, 140.44, 129.61, 124.18; LCMS: m/z: 377.14.

6b: Yield (89%); δ 7.91 (1H), 7.79 – 7.37 (m, 4*H*), 7.13 (dd, 2H), 7.00 – 6.60 (m, 2H), 6.36 (d, 1*H*), 5.11 (s, 2H), 4.26 (t, 1H), 4.09 – 3.93 (m, 3H), 2.18 (tt, 2H). δ 162.26, 156.24, 140.44, 137.70, 127.77, 114.01, 102.34, 67.14; LCMS: m/z: 422.12.

6c: Yield (91%); δ 8.14 (d, *J* = 7.5 Hz, 2H), 8.04 – 7.45 (m, 3H), 7.16 (d, 2H), 7.02 – 6.48 (m, 2H), 6.37 (d, 1H), 5.14 (s, 2H), 4.68 – 3.66 (m, 4H), 2.23 (p, 2*H*). δ 172.34, 164.71, 158.59, 146.20, 140.44, 116.47, 100.25; LCMS: m/z: 422.12.

6d: Yield (91%); δ 9.63 (s, 2H), 7.75 (dd, *H*), 7.59 (s, H), 7.13 – 6.65 (m, H), 6.41 (d, H), 5.23 (s, H), 4.31 – 3.17 (m, H), 2.52 – 0.95 (m, H). δ 162.23,161.79, 156.24, 149.51, 143.07, 129.61, 124.18, 122.03, 120.75; LCMS: m/z: 407.15.

6e: Yield (93%); δ 9.63 (s, 2H), 7.77 (dd, H), 7.57 (s, H), 7.12 – 6.67 (m, H), 6.41 (d, H), 5.23 (s, H), 4.31 – 3.17 (m, H), 2.52 – 0.96 (m, H). δ 162.21, 161.82, 156.24, 150.63, 149.51, 140.44, 122.03, 120.75; LCMS: m/z: 407.15.

6f: Yield (90%); δ 9.63 (s, 2H), 7.77 (dd, H), 7.55 (s, H), 7.13 – 6.65 (m, H), 6.41 (d, H), 5.23 (s, H), 4.31 – 3.17 (m, H), 2.52 – 0.94 (m, H). δ 162.23,161.81, 150.65, 149.51, 143.07, 124.18, 122.03; LCMS: m/z: 407.15.

6g: Yield (88%); δ 7.73 (d, 1H), 7.64 – 7.50 (m, 2H), 7.11 (dd, 2H), 6.96 – 6.81 (m, 3H), 6.75 (d, 1H), 6.35 (d, 1*H*), 5.12 (s, 2*H*), 4.35 – 3.82 (m, 4H), 2.41 – 2.03 (m, 5H). δ 162.26, 161.82, 156.24, 143.07, 130.20, 129.54, 127.60; LCMS: m/z: 391.15.

6h: Yield (94%);δ 7.87 – 7.58 (m, 3H), 7.18 (t, 1*H*), 6.80 (dddd, 5H), 6.37 (d, 1*H*), 5.14 (s, 2H), 4.25 (t, 1H), 4.07 (dt, 3H), 2.50 – 1.94 (m, 5H). δ 162.25, 161.82, 159.22, 156.24, 143.07, 140.44, 138.74, 129.61.; LCMS: m/z: 391.15.

6i: Yield (86%);δ 7.71 (d, 3H), 7.59 (s, 5H), 7.24 (d, 6H), 6.84 (ddd, 12H), 6.38 (d, 3H), 5.13 (s, 6H), 4.40 – 3.76 (m, 12H), 2.21 (tt, 6H). δ 162.16, 161.83, 159.21, 156.24, 143.07, 140.44, 129.61; LCMS: m/z: 411.10.
6j: Yield (82%); δ 7.65 (dd, 3H), 7.32 (d, 1H), 7.14 (dd, 1H), 6.83 (ddd, 3H), 5.11 (s, 2H), 4.43 – 3.81 (m, 4H), 2.36 – 1.91 (m, 2H). δ 162.22, 161.81, 143.07, 140.44, 130.78, 124.18, LCMS: m/z: 445.06.

CONCLUSION

In summary, the synthesis of some novel wholly reliable strategy to afford novel chromen-2-ones coupled with 1,2,3-Triazoles via key 1,3-dipolar cycloaddition approach using ultrasound technique was described, All the compounds were investigated for in vitro anticancer activity on three cell lines which include the MCF-7, A-549, HeLa and the results revealed that three compounds 6c, 6f, and 6j were displayed most promising activity against three cell lines as compared to the etoposide.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

Jagadeesh Kumar Ega http://orchid.org/0000-0001-5837-4580
Prashanth Raja Peddapyata http://orchid.org/0000-0003-4236-8770
Kavitha Siddoju http://orchid.org/0000-0001-5808-708X

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