RASĀYAN *J. Chem.*
Vol. 17 | No. 1 |128-137| January - March | 2024
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

SYNTHESIS AND CHARACTERIZATION OF NEW NILUTAMIDE NO_2 GROUP MODIFIED 1,2,3-TRIAZOLES AS *In vitro* ANTICANCER AGENTS

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ABSTRACT

Nilutamide (1) of the NO2 group can be converted to NH2 by addition of triethyl silane and Wilkinson's catalyst to give amino compound (2) via reduction. It is further treated with t_BuONO by TMSN3 in RB flask containing CH3CN to give 3-(4-(4-azido-3-(trifluoromethyl) phenyl)-5-5-dimmethylimidazolidine-2,4-dione (3). Azide furthermore reacted with different terminal alkynes in the presence of Sharpless catalyst to form 5,5-dimethyl-3-(4-(4-phenyl-1H-1,2,3-triazol-1-yl)-3-trifluoromethyl imidazolidine-2,4-diones(4a-4j) with favorable yields depicted (scheme-I) in this manuscript. All the compounds were screened for in vitro anti-cancer activity, among them compound 4h containing the 4-CN group showed highest anticancer activity PC3=-1.94±1.16µM and DU-145=1.54±0.32 and MCF-7=1.43±0.92 µM. Compound 4d NO2 group resulting compound 4d exhibited PC3 3.38±2.07 and DU-145 =3.58±1.57 µM. Compound 4C containing Ome group PC3=2.10±1.38, DU-145=1.57±0.32 and MCF-7=2.08±1.64 µM as IC50 in µM, Etoposide is used as a reference.

Keywords: 1,2,3-triazoles, cyclo addition, Sharpless catalyst, Anticancer activity, Etoposide, Nilutamide, Wilkinson's catalyst, 5,5-dimethyl-3-(4-(4-phenyl-1H-1,2,3-triazol-1-yl)-3-(trifluoromethyl) phenyl) imidazolidine-2,4-dione,3P5DMI=3-(4-azido-3-(trifluoromethyl) phenyl) -5,5-dimethylimidazoline-2,4-dione)

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INTRODUCTION

Malignancy poses a significant global health challenge, leading to a substantial increase in the number of affected patients worldwide.[1,2] One crucial aspect of this challenge is the role of malignancy as a choosy adversary of androgen receptor, effectively inhibiting influence of androgenic hormone like testosterone and dihydrotestosterone inside body.[3-5] Prostate cancer cells heavily trust on hormones aimed at their development and existence. Considering this, Nilutamide emerges as a promising therapeutic agent capable of slowing down the progression of prostate cancer, potentially extending the survives of those suffering from this ailment.[6-7] Given the vital roles played by testosterone and dihydrotestosterone in the growth and survival of prostate cancer cells, Nilutamide represents a valuable tool for halting the advancement of the disease, representing a pivotal development in the m\anagement of less severe cases.[8-9] In line with our ongoing research endeavors, we have formulated a synthesis pathway to produce a novel compound referred to as 5,5-dimethyl-3-(4-(4-phenyl-1H-1,2,3-triazol-1-yl)-3-(trifluoromethyl) phenyl) Imidazolidine-2,4-dione.[10-11] This synthesis process encompasses three distinct steps and is expected to yield a high-quality product. A 1,2,3-triazole scaffold is a compelling nitrogen-comportment heterocyclic framework that has originated wide bids.[12-16]

EXPERIMENTAL

Material and Methods

No further purification was carried out on the commercially available chemicals and reagents. Transparency of the composites was assessed (TLC) employing Merck 60F254 silica gel plates. 1H and 13C NMR spectra be documented using a MPS, with chemical shifts reference to tetramethyl silane. ESI Mass spectra be situated generated by a Shimadzu QP5050A quadrupole-based Mass Spectrometer. Fundamental studies conducted utilizing Carlo Ebra 106 and Perkin Elmer Model 240 analysers. The 1H and 2H-1,2,3-triazoles are aromatic and in equilibrium with each other in solution as well as a gas phase, while 4H-1,2,3-triazoles,

http://doi.org/10.31788/RJC.2024.1718679

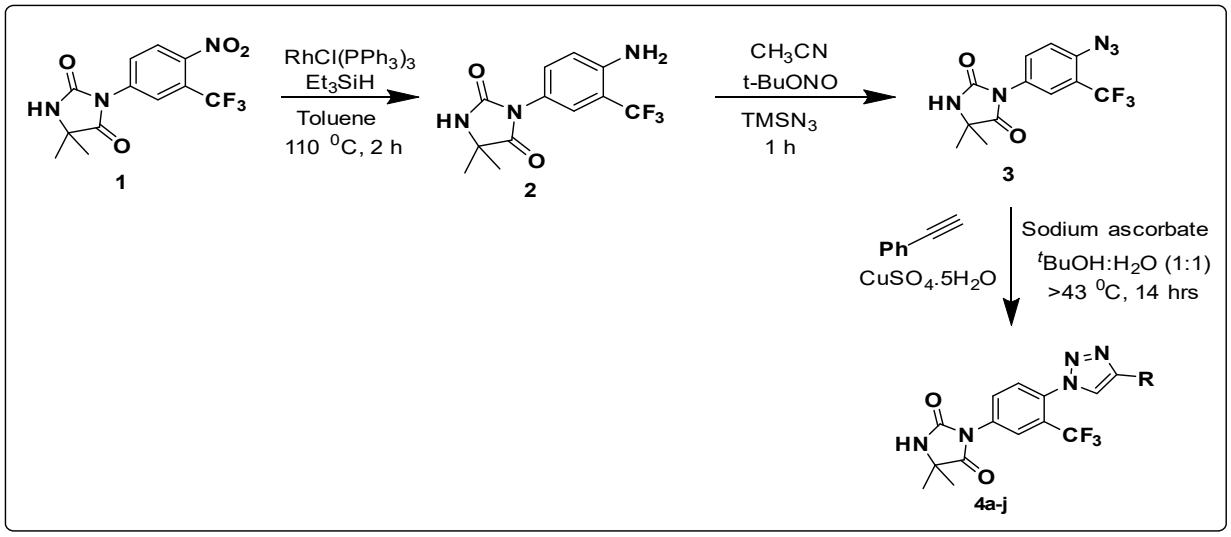
1H-1,2,3-triazole is as prevailing scaffold and extensively existing in therapeutic agents and has gained more interest due to its medicinal chemistry applications.

RESULTS AND DISCUSSION

In the first step nitro group of Nilutamide (1) is treated with triethyl silane and Wilkinson's catalyst at 110^0C, 2 h to give amine product (2) as reference cited.[10] Amine-200 milli grams, 2.14 milli mol) be situated thawed in MeCN [4 milli liter] in 25 ml RBF and chilled to 0°C in ice bath. Into this, t-BuONO (331 milli gram, 380 micro liter, 3.21 milli mole), stirred mixture was additional followed through TMSN3 (300 milli gram, 340 micro liter, 2.56 milli mole) drop-wise, solution obtained be situated agitated by ambient room temperature for a duration of 1 hour.[11]Afterward, the reaction mix was subjected to void concentration, unrefined produce underwent refinement across silica gel chromatography by means of hexane as eluent. This process yielded azide (3) as the final product of the second step.

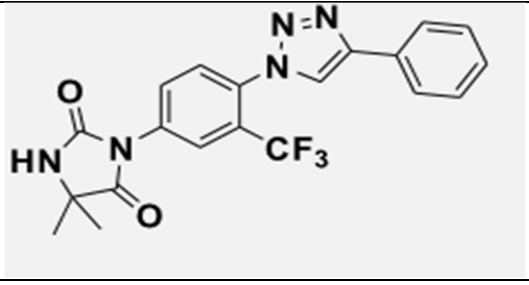
Normal process for synthesis of 5,5-dimethyl-3-(4-(4-phenyl-1H-1,2,3-triazol-1-yl)-3-(trifluoromethyl) imidazolidine-2,4-diones (4a-4j)

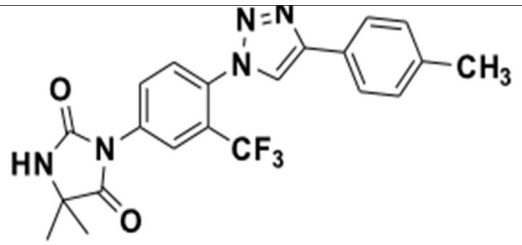
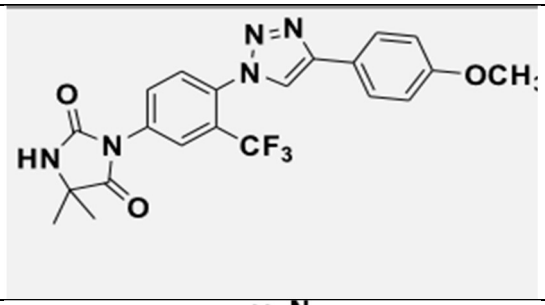
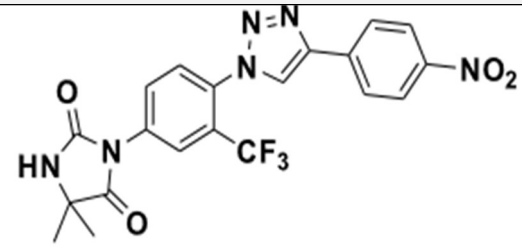
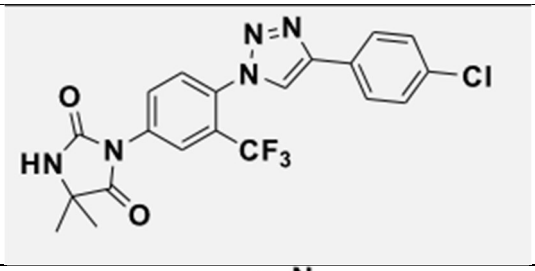
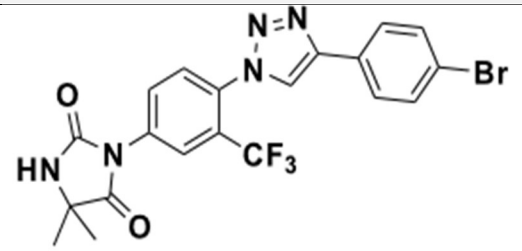
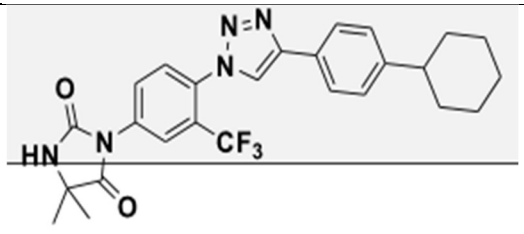
In a RB Flask 100 mL, a reaction mixture was prepared as follows: 0.102 grams (1 mmol) of phenylacetylene, 0.48 grams (1.2 mmol) of compound (3), 0.025 grams (10 mol%) of CuSO4.5H2O, and 0.0396 grams (0.2 mmol) of sodium ascorbate were combined in 5 mL of a tBuOH/H2O (1:1) solution. Resulting mix was heated to 43°C and allowed to react pro 14 hours. advancement of reaction be supervised by TLC. Afterwards, end of reaction, mix be mined two times by 10 ml portions of a water-ethyl acetate mixture. organic film be situated then desiccated by means of Na2SO4, riddled to remove any solids, and extra solvent was detached by concentrating it beneath a rotary evaporator. Crude product obtained stood extra cleaned by column chromatography. An eluent mixes of ethyl acetate and hexane in a 1:1 ratio was used for this purpose. This process yielded the pure product 4a in a respectable 80% yield. This procedure was repeated similarly to synthesize the remaining compounds in the study.[12-13]



Scheme-1

Table-1: Structures and Yield %of compounds

Entry	Name	Structure	Yield(%)
4a	5,5-dimethyl-3-(4-(4-phenyl-1H-1,2,3-triazol-1-yl)-3-(trifluoromethyl)phenyl)imidazolidine-2,4-dione		80%

4b	5,5-dimethyl-3-(4-(4-(p-tolyl)-1H-1,2,3-triazol-1-yl)-3-(trifluoromethyl)phenyl)imidazolidine-2,4-dione		82%
4c	3-(4-(4-(4-methoxyphenyl)-1H-1,2,3-triazol-1-yl)-3-(trifluoromethyl)phenyl)-5,5-dimethylimidazolidine-2,4-dione		75%
4d	5,5-dimethyl-3-(4-(4-(4-nitrophenyl)-1H-1,2,3-triazol-1-yl)-3-(trifluoromethyl)phenyl)imidazolidine-2,4-dione		84%
4e	3-(4-(4-(4-chlorophenyl)-1H-1,2,3-triazol-1-yl)-3-(trifluoromethyl)phenyl)-5,5-dimethylimidazolidine-2,4-dione		83%
4f	3-(4-(4-(4-bromophenyl)-1H-1,2,3-triazol-1-yl)-3-(trifluoromethyl)phenyl)-5,5-dimethylimidazolidine-2,4-dione		84%
4g	3-(4-(4-(4-cyclohexyl phenyl)-1H-1,2,3-triazol-1-yl)-3-(trifluoromethyl)phenyl)-5,5-dimethylimidazolidine-2,4-dione		68%

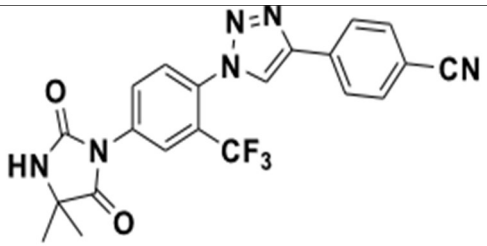
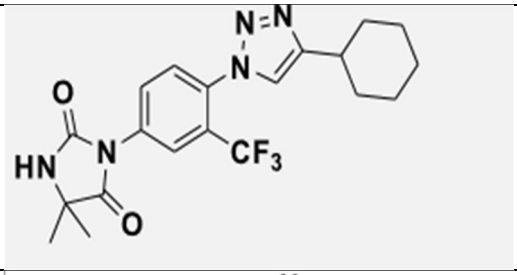
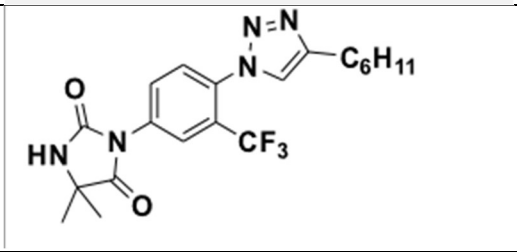
4h	4-(1-(4-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl) benzonitrile		73%
4i	3-(4-(4-cyclohexyl-1H-1,2,3-triazol-1-yl)-3-(trifluoromethyl)phenyl)-5,5-dimethylimidazolidine-2,4-dione		65%
4j	3-(4-(4-(hexa-1,3,5-triyn-1-yl)-1H-1,2,3-triazol-1-yl)-3-trifluoromethyl) phenyl)-5,5-dimethylimidazolidine-2,4-dione		62%

Table-2: Physical data and analytical data of compounds

Entry	Melting point. ^{o}C	Molecular Formula	Found (%) (Calculated)		
			C	H	N
4a	192	$C_{20}H_{16}F_3N_5O_2$	57.95 (57.83	3.89 3.88	16.88 16.86)
4b	194	$C_{21}H_{18}F_3N_5O_2$	58.84 (58.74	4.24 4.23	16.33 16.31)
4c	195	$C_{21}H_{18}F_3N_5O_3$	56.75 (56.63	4.08 4.07	15.78 15.72)
4d	202	$C_{20}H_{15}F_3N_6O_4$	52.30 (52.18	3.29 3.28	18.28 18.26)
4e	196	$C_{20}H_{15}ClF_3N_5O_2$	53.54 (53.40	3.37 3.36	15.59 15.57)
4f	210	$C_{20}H_{15}BrF_3N_5O_2$	48.72 (48.60	3.07 3.06	14.19 14.17)
4g	201	$C_{26}H_{26}F_3N_5O_2$	62.89 (62.77	5.28 5.27	14.10 14.08)
4h	197	$C_{21}H_{15}F_3N_6O_2$	57.39 (57.27	3.44 3.43	19.10 19.08)
4i	204	$C_{20}H_{22}F_3N_5O_2$	57.12 (57.00	5.27 5.26	16.64 16.62)
4j	202	$C_{20}H_{22}F_3N_5O_2$	57.12 (57.00	5.27 5.26	16.64 16.62)

Table-3: 1H and 13C-NMR data

S. No.	1 H NMR (300 MHz, CDCl3) (ppm)	13 CNMR (75 MHz, DMSO-d6) (ppm)
4a	9.37 (s, 1H), 8.87 (s, 1H), 8.33 (s, 1H), 8.10 (s, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.52 – 7.22 (m, 3H), 5.57 (s, 1H), 1.52 (s, 6H).	176.89, 155.82, 154.38, 133.82, 132.00, 131.19, 130.98, 130.41, 129.17, 128.86, 123.79, 127.11,126.66, 126.28, 125.77, 125.02, 124.53, 122.93,120.83, 58.82, 24.75.
4b	8.87 (s, 1H), 8.32 (d, J = 7.5 Hz, 1H), 8.22 – 7.99 (m, 2H), 7.56 (d, J = 7.5 Hz, 2H), 7.29	176.89, 155.82, 154.38, 136.14, 134.39, 133.73,132.00, 131.40, 131.19, 130.98, 130.75,

	(d, J = 7.5 Hz, 2H), 5.57 (s, 1H), 2.34 (s, 3H), 1.52 (s, 6H).	130.31,129.20, 128.90, 127.11, 126.60, 126.37, 124.53,122.93, 120.83, 58.82, 24.75, 21.12.
4c	8.35 (d, J = 8.9 Hz, 1H), 8.21 – 7.95 (m,2H), 7.69 – 7.44 (m, 3H), 7.03 (d, J = 7.5 Hz, 2H), 5.09 (s, 1H), 3.82 (s, 3H), 1.47 (s,6H).	176.89, 159.63, 155.82, 154.38, 134.23, 133.79,132.00, 131.19, 130.98, 129.09, 126.70, 125.92,125.02, 124.57, 122.93, 120.83, 114.40, 58.82,56.03, 24.75.
4d	9.34 (s, 1H), 8.30 (d, J = 7.4 Hz, 3H), 8.16 – 7.73 (m, 4H), 5.60 (s, 1H), 1.52 (s, 6H).	176.89, 155.82, 154.38, 146.40, 134.60, 134.28,133.73, 132.00, 131.40, 131.19, 130.98, 130.75,129.03, 126.66, 125.02, 124.81, 124.45, 122.93,120.83, 58.82, 24.75.
4e	9.33 (s, 1H), 8.87 (s, 1H), 8.31 (d, J = 8.9 Hz, 1H), 8.09 (d, J = 7.5 Hz, 1H), 7.49 (dd, J = 54.2, 7.5 Hz, 4H), 5.57 (s, 1H), 1.52 (s, 6H).	176.89, 155.82, 154.38, 134.39, 134.14, 133.73,132.00, 131.19, 130.98, 129.56, 129.20, 128.28,127.11, 126.60, 125.02, 124.53, 122.93, 120.83,58.82, 24.75.
4f	9.34 (s, 1H), 8.87 (s, 1H), 8.31 (d, J = 8.9 Hz, 1H), 8.09 (d, J = 7.3 Hz, 1H), 7.55 (dd, J = 51.8, 7.5 Hz, 4H), 5.57 (s, 1H), 1.52 (s, 6H).	176.89, 155.82, 154.38, 134.33, 133.79, 132.37,132.00, 131.19, 130.98, 129.09, 128.37, 127.48,126.60, 125.02, 124.53, 123.35, 122.93, 120.83,58.82, 24.75.
4g	8.29 (s, 1H), 8.19 – 7.89 (m, 2H), 7.81 (d,J = 8.9 Hz, 1H), 7.50 (dd, J = 83.5, 7.5 Hz,4H), 5.59 (s, 1H), 2.86 (dd, J = 16.2, 7.7Hz, 1H), 2.22 – 1.94 (m, 2H), 1.82 (dt, J =19.8, 10.1 Hz, 2H), 1.69 – 1.55 (m, 6H), 1.52 (s, 6H).	176.89, 155.82, 154.38, 146.52, 134.33, 133.82, 132.00, 131.58, 131.19, 130.98, 130.75, 129.20, 127.11, 126.60, 125.02, 124.45, 122.93, 120.83, 58.82, 42.15, 32.61, 25.91, 24.84.
4h	9.43 (s, 1H), 8.88 (s, 1H), 8.33 (d, J = 7.5Hz, 1H), 8.10 (d, J = 7.5 Hz, 1H), 7.78 (q,J = 7.6 Hz, 4H), 5.57 (s, 1H), 1.52 (s, 6H).	176.89, 155.82, 154.38, 134.39, 133.73, 132.48,132.00, 131.19, 130.98, 130.14, 129.20, 127.11,126.70, 125.27, 125.02, 124.53, 122.93, 119.12,113.07, 58.82, 24.75.
4i	8.35 (d, J = 8.9 Hz, 1H), 8.08 (s, 1H), 7.97(s, 1H), 7.68 (s, 1H), 5.11 (s, 1H), 3.44 (t, J= 7.8 Hz, 1H), 2.46 (dd, J = 13.5, 5.7 Hz,2H), 1.66 (dd, J = 23.2, 9.8 Hz, 8H), 1.47 (s, 6H).	176.89, 157.54, 155.82, 134.33, 133.82, 132.00,131.19, 130.98, 129.20, 127.11, 126.70, 126.45,125.02, 122.93, 120.83, 58.82, 37.20, 32.14,25.91, 24.75.
4j	8.46 (s, 1H), 8.08 (s, 3H), 5.59 (s, 1H),2.76 (t, J = 8.0 Hz, 2H), 1.70 (p, J = 7.8Hz, 2H), 1.52 (s, 6H), 1.46 – 1.26 (m, 6H),0.99 (t, J = 6.4 Hz, 3H).	176.89, 155.82, 154.52, 134.23, 133.82, 132.00,131.19, 130.98, 129.14, 127.11, 126.66, 125.21,125.02, 122.93, 120.83, 58.82, 31.64, 29.23,27.81, 26.72, 24.75, 22.93, 14.01.

Analytical Discussion

***in-vitro* anticancer action**

In the study, newly finished Nilutamide (with a NO2 group) improved 1,2,3-triazoles (designated as 4a-4j) were subjected to *in-vitro* anticancer action assessments counter to three dissimilar malignance cell outlines, viz. PC3, and MCF-7, DU-145. These evaluations were performed using the MTT assay, with the well-established chemotherapeutic drug Etoposide serving as the standard for comparison. Among the compounds tested, two specific compounds, 4c and 4h, demonstrated exceptional anti-cancer activities against all three cell outlines, PC3, and MCF-7, DU-145. This indicates their potential as promising candidates for further investigation and development as anti-cancer agents. Furthermore, two other compounds, 4d and 4j, exhibited noteworthy anti-cancer activity, particularly against the PC3 and DU-145 cell lines. In fact, their efficacy against these two specific cell lines was found to be superior to that of Etoposide, which is a widely recognized chemotherapeutic drug. This suggests that 4d and 4j hold significant promise for targeted treatments against PC3 and DU-145 cancers.

Overall, these findings highlight the potential of Nilutamide modified 1,2,3-triazoles, specifically compounds 4c, 4h, 4d and 4j, as promising candidates for further research and development in the field of cancer therapy due to their impressive in vitro anticancer activities. Further studies and clinical trials stand warranted to explore their worth and care profiles for potential use in cancer treatment.

Regenerate

Accuracy of Compound 4h containing the 4-CN group presented the peak anticancer action (PC3 = 1.94±1.16μM, DU-145 = 1.54±0.32 and MCF-7=1.43±0.92 μM). Compound 4d NO2 group resulting compound 4d exhibited (PC3 3.38±2.07 and DU-145 = 3.58±1.52μM). Compound 4c contains an OMe group (PC3 2.10±1.38, DU-145 = 1.57±0.32 and MCF-7=2.08±1.64μM).

Table-4: Anticancer activity results of newly synthesized 4a-4j with IC50 in μM

Entry	[c]PC3	[d]DU-145	[e]MCF-7
4a	5.56±3.71	6.14±4.10	10.54±5.98
4b	8.67±4.98	8.47±3.26	ND
4c	2.10±1.38	1.57±0.32	2.08±1.64
4d	3.38±2.07	3.58±1.52	ND
4e	13.52±6.72	ND	14.4±5.62
4f	17.58±8.42	ND	24.6±9.82
4g	ND	7.14±3.04	10.9±4.36
4h	1.94±1.16	1.54±0.32	1.43±0.92
4i	3.92±2.31	3.67±1.48	14.86±5.92
4j	2.26±1.50	1.69±0.41	15.40±5.59
etoposide	2.39 ± 1.56	1.97 ± 0.45	2.11 ± 0.024

ND=Not determine.
[a] each data represents as mean ±S.D values.
[b] from three different experiments performed in triplicates.
[c] PC: human prostate cancer cell line.
[d] DU-145:human prostate cancer cell line.
[e] MCF-7: human breast cancer cell line.

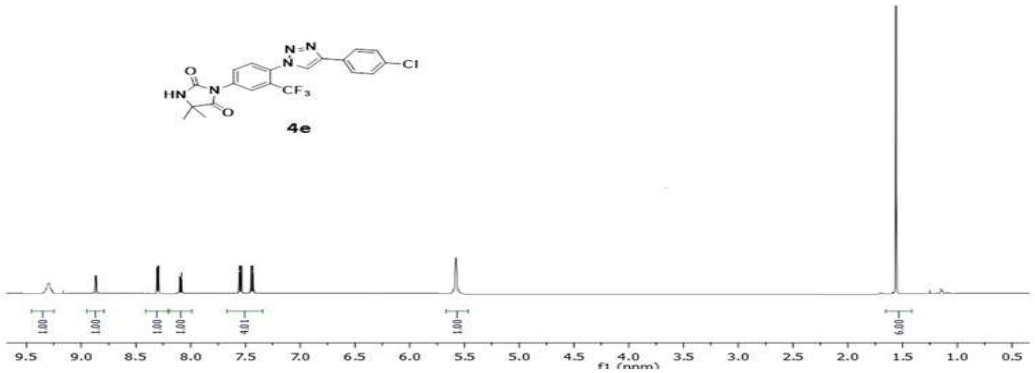


Fig.- 1: IHNMR band of the composite 4e

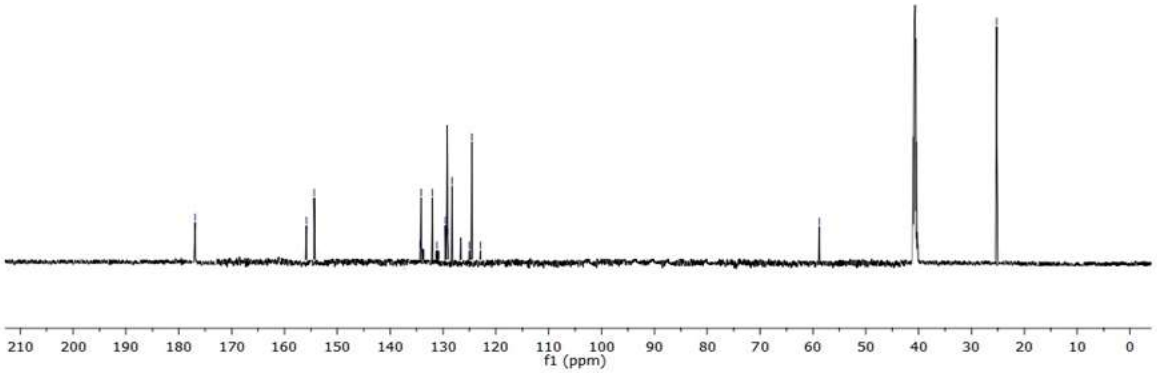


Fig.-2:13 CNMR spectrum of the compound 4e

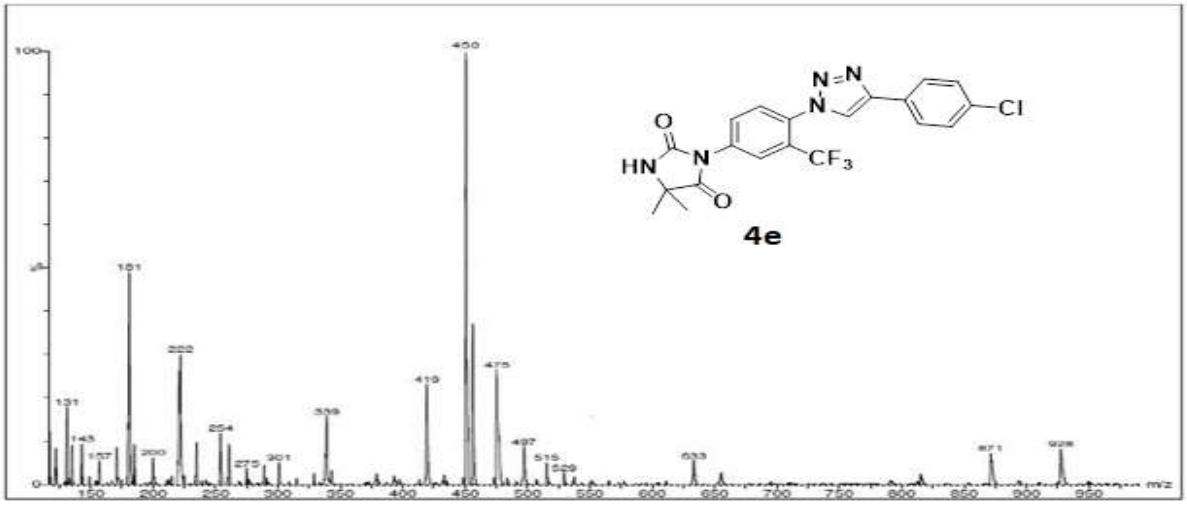


Fig.-3: Mass spectrum of the compound 4e

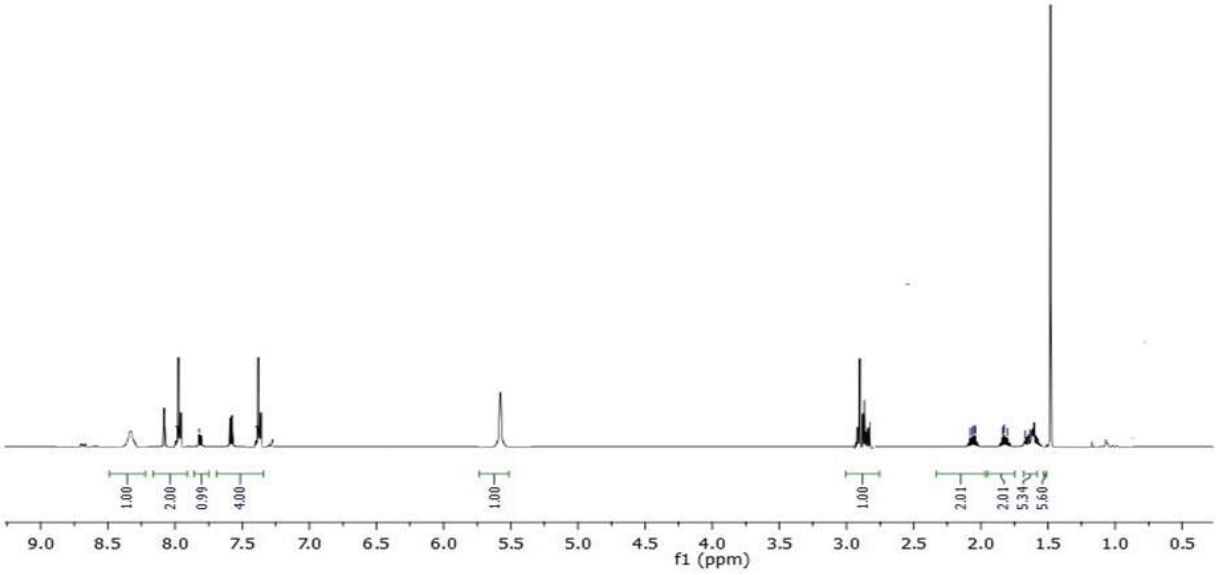


Fig.-4: ^{1}HNMR spectrum of the compound 4g

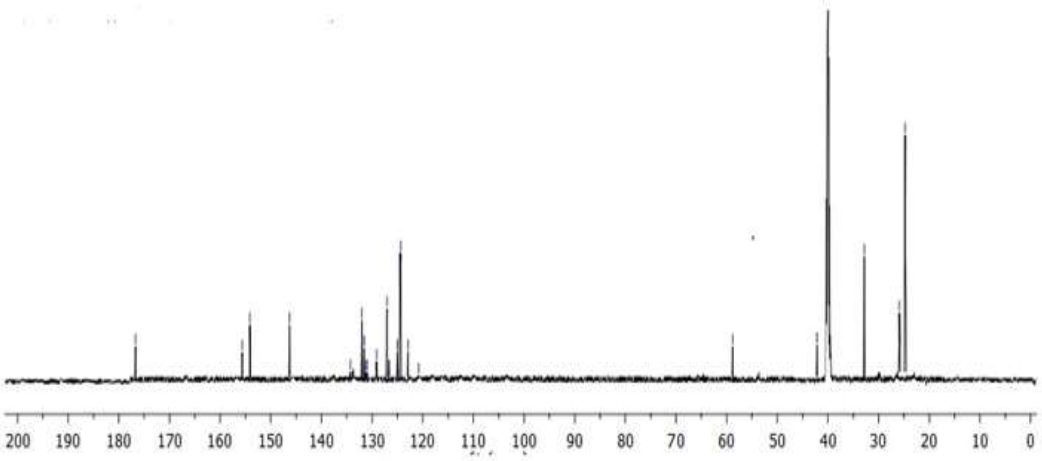


Fig.-5: 13 CNMR spectrum of the compound 4g

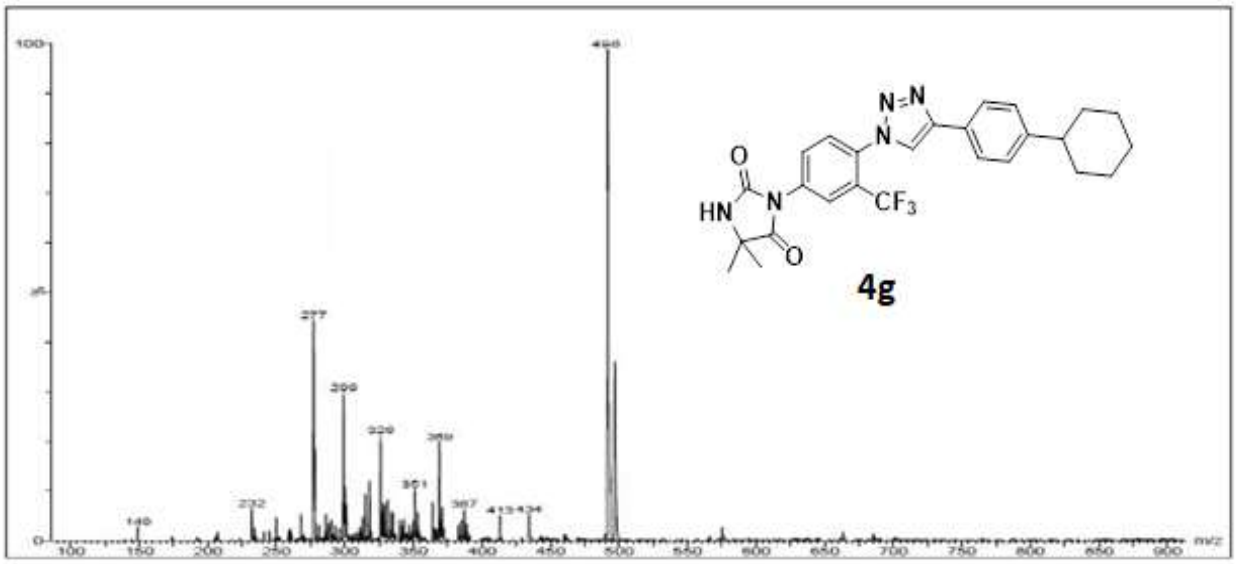


Fig.- 6: Mass spectrum of the compound 4g

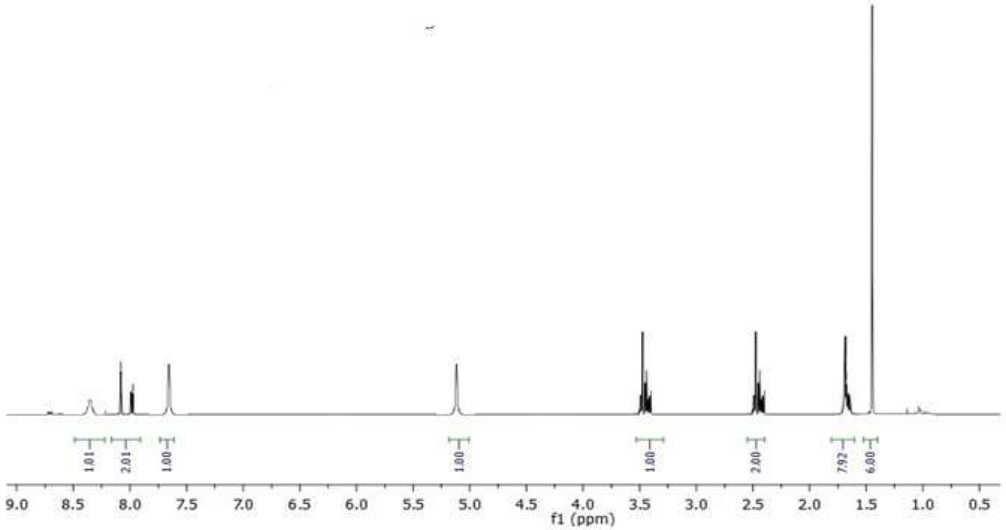


Fig.-7: 1HNMR spectrum of the compound 4i

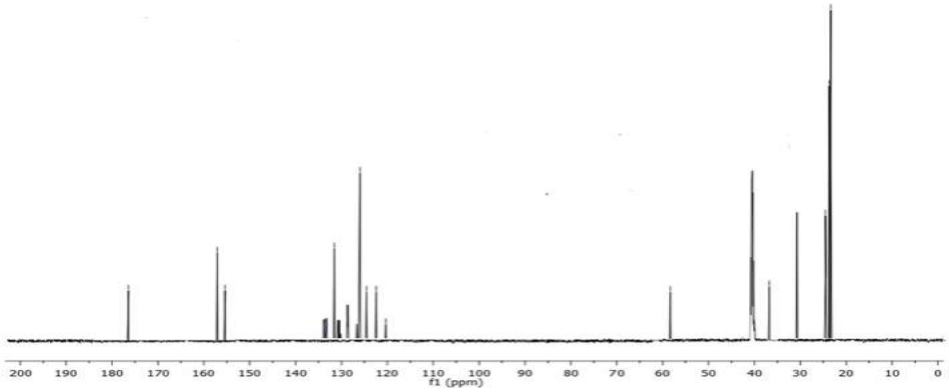


Fig.-8: 13CNMR spectrum of the compound 4i

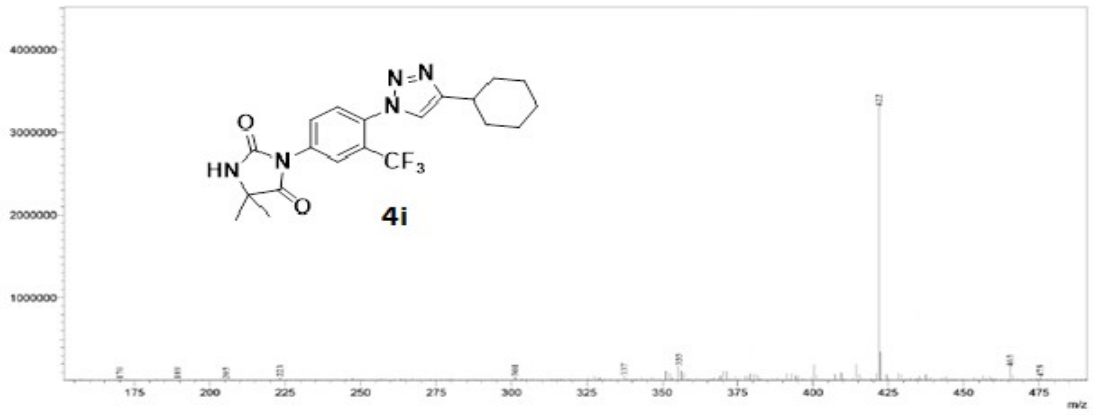


Fig.-9: Mass spectrum of the compound 4i

CONCLUSION

In the present investigation, we have successfully synthesized a novel compound, namely, 5,5-dimethyl-3-(4-(4-Phenyl-1H-1,2,3-Triazol-1-yl)-3-(trifluoromethyl) (I,2,4-DImidazolidine-2,4-dione), with remarkable yields and exceptional purity. Specifically, the title compounds 4c, 4d, 4h, and 4j have demonstrated significant anti-cancer properties, showcasing their potential in the field of oncology research.

ACKNOWLEDGMENTS

We extend our heartfelt appreciation to the chemistry department at Chaitanya Deemed to be University in Hanamkonda, as well as the Department of Chemistry within the School of Sciences at SR University in Warangal, Telangana. We are grateful for the invaluable laboratory facilities and resources provided, which enabled us to carry our study endeavors.

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 ID has given below.

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[RJC-8679/2023]