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SYNTHESIS AND BIOLOGICAL ACTIVITY OF NOVEL QUINOLINE AND COUMARIN HYBRIDS BRIDGED BY 1,2,3-TRIAZOLE RING

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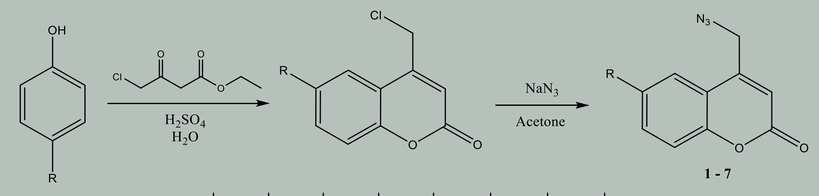
INTRODUCTION

The field of drug discovery is constantly advancing in its quest to find new biologically active compounds. Recently, an emerging trend in medical chemistry is molecular hybridization, which is often used as a key strategy in drug design.[1] It includes combining known biologically active moieties as scaffolds to build a new molecule that could retain properties, or potentially have new activity. Coumarin and quinoline are widely used in pharmaceuticals, as well as in new molecular hybrids. Triazole ring are also important linkage, building block and pharmachophore in molecular hybrids with quinolines and coumarins.[2,3]

Chemistry

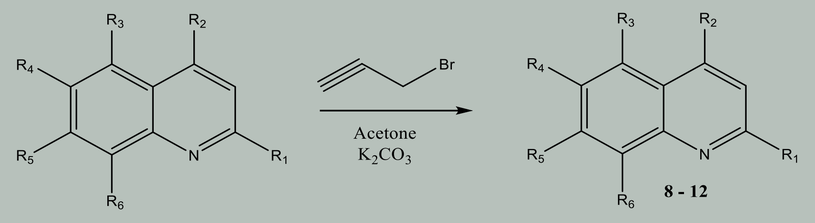
In this work, we present synthesis of novel quinoline and coumarin hybrids bridged with 1,2,3-triazole ring. The methylazido coumarins were prepared by cyclization of corresponding phenols and ethyl 4-chloroacetoacetate, followed by azidation reaction. The hybrids bridged with 1,2,3-triazole (13-51) were prepared using Cu-catalyzed Huisgen-1,3-dipolar cycloaddition reaction.

Synthesis of methylazido coumarins



	1	2	3	4	5	6	7
R	OH	OMe	F	$C(CH_3)_3$	OEt	Cl	Br

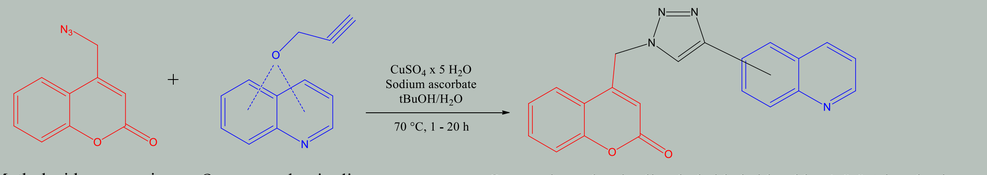
Synthesis of hydroxypropynyl quinolines



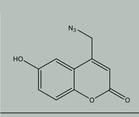
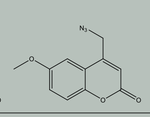
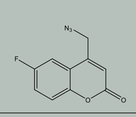
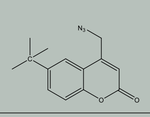
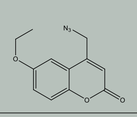
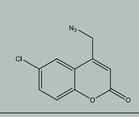
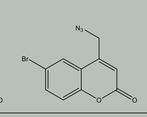
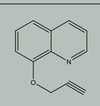
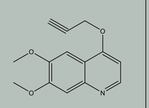
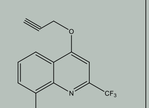
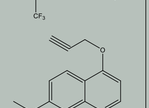
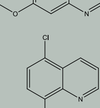
One of the R substituents is an OH group, which is converted into a propargyl one.

	R_1	R_2	R_3	R_4	R_5	R_6
8	H	H	H	H	H	
9	H		H	OMe	OMe	H
10	CF_3		H	H	H	CF_3
11	H		H	H	OMe	H
12	H	H	Cl	H	H	

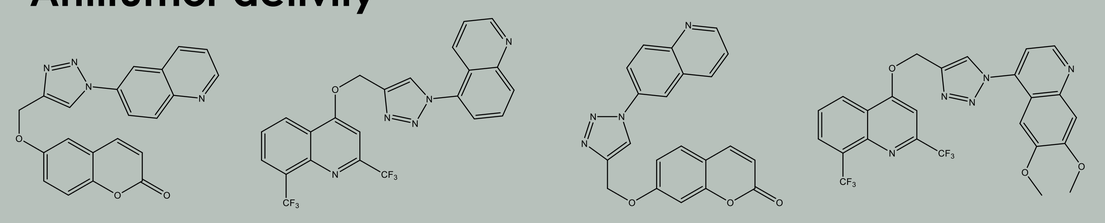
Synthesis of triazole linked hybrids



Methylazido coumarin *O*-propargyl quinoline Coumarin and quinoline hybrids bridged by 1,2,3-triazole ring

							
	13	14	15	16	17	18	19
	20	21	22	23	24	25	26
	27	28	29	30	31	32	33
	34	35	36	37	38	39	40
	41	42	43	44	45	46	47

Antitumor activity



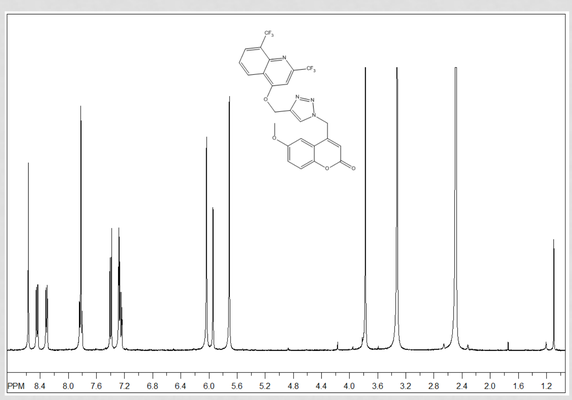
48 **49** **50** **51**

Compound / Cell line	Capan-1 pancreatic adenocarcinoma µM	DND-41 acute lymphoblastic leukemia µM	HL-60 acute myeloid Leukemia µM	Z-138 non-Hodgkin Lymphoma µM
48	27,4	28,0	49,6	25,5
49	>100	48,7	41,1	27,8
50	68,7	73,1	68,5	68,9
51	40,8	22,3	>100	39,9

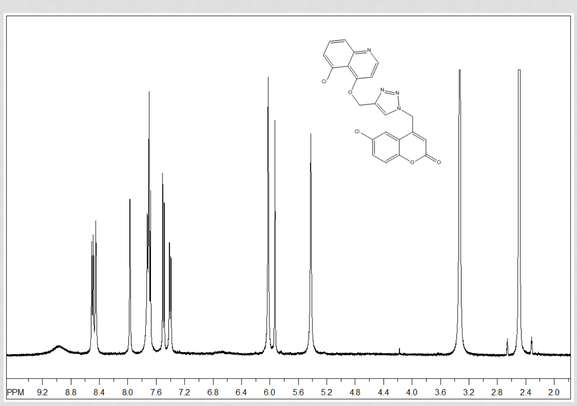
Antitumor activities of novel molecular hybrids were examined against human tumor cell lines: glioblastoma, pancreatic adenocarcinoma, colorectal carcinoma, lung carcinoma, acute lymphoblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia and non-Hodgkin lymphoma.

Conclusion

The coumarin and quinoline hybrids bridged with 1,2,3-triazole ring (13-51) were prepared by Cu-catalyzed click reaction of corresponding terminal alkyne and azide. Of all evaluated compounds hybrid 51 showed the moderate activity (22.3 µM) against acute lymphoblastic leukemia cells (DND-41)



^{1}H NMR spectrum of compound 28



^{1}H NMR spectrum of compound 46

Literature
1. G. Bérubé, *Expert Opinion on Drug Discovery* 2016, *11*, 281–305.
2. R. Reddyrajula. U. Dalimba, *Chemistry Select.* 2019, *4*, 2685–2693.
3. K. Bhagat et. al. *ACS Omega* 2019, *4*, 8720–8730.

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