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SYNTHESIS OF CONJUGATED ISATIN-BENZOFURAN HYBRIDS AS POTENTIAL CHEMOTHERAPEUTIC AGENTS AGAINST COLORECTAL CANCER

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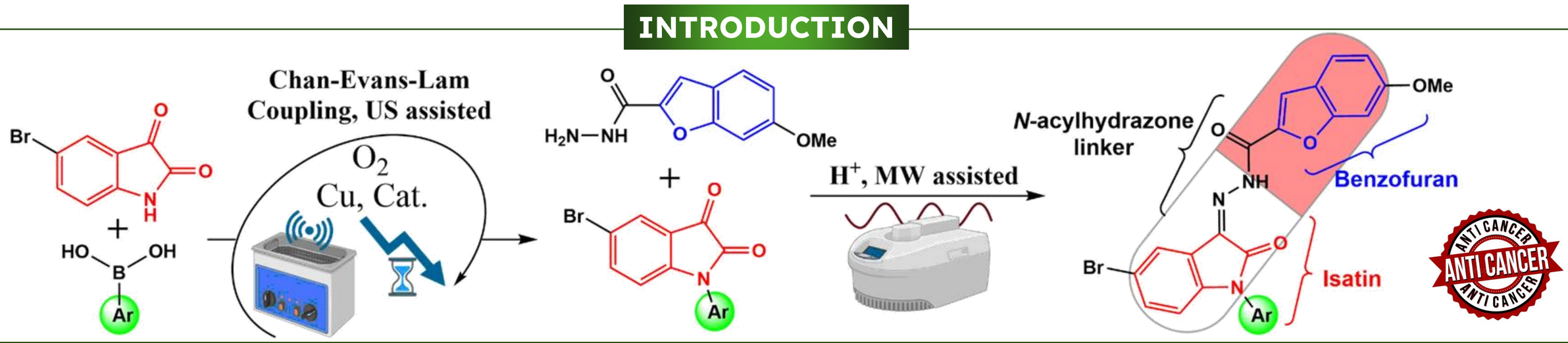
ABSTRACT

Colorectal cancer is the third most common type of cancer and the second in mortality worldwide (WHO). benzofuran and isatin are heterocycles found in a wide variety of natural and synthetic molecules with potent anticancer activity, as well as the *N*-acylhydrazone fragment. Molecular hybridization is a strategy that has been shown to significantly improve pharmacological properties by chemically linking two bioactive units into a new entity. In this work, a serie of isatin-benzofuran conjugated hybrids with an *N*-acylhydrazone linker were synthesized, varying the substitution pattern of an aryl group at the *N*-1 position of the isatin core. The benzofuran fragment was constructed through microwave-assisted Rap-Stoermer reaction, while structural diversification of 5-bromo isatin was achieved via *N*-arylation using Chan-Evans-Lam cross-coupling, catalyzed by Cu(II), under optimized reaction conditions employing ultrasound as an energy source. This led to a significant reduction in reaction time and an increase in yield. The final step involved condensation to form the acylhydrazone-type linker, also assisted by microwaves, resulting in good yields. The synthesis of the target molecules was confirmed by ^{1}H and ^{13}C NMR.

INTRODUCTION



METHODOLOGY

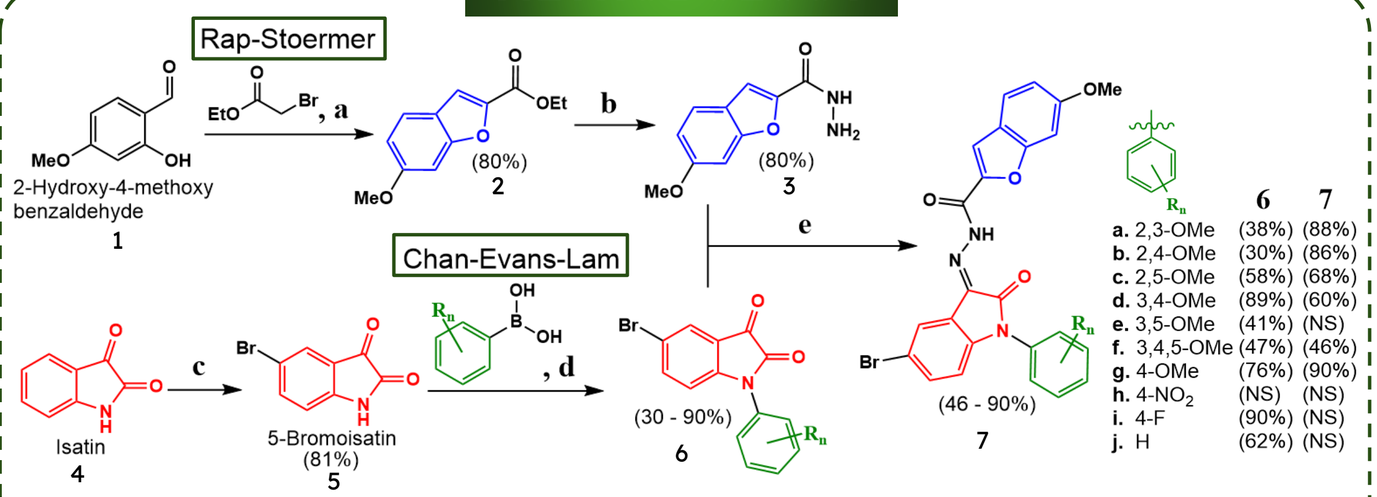


Figure 1. Synthesis of isatin-benzofuran conjugated hybrid derivatives. a) K_2CO_3, DMF, MW, 160°C, closed vessel, 50 min [1]. b) NH_2-NH_2.H_2O, EtOH, reflux, 80°C, 24 h [2]. c) pyridinium bromochromate, AcOH, stirring, 90°C, 30 min [3]. d) Table 1. e) AcOH, EtOH, MW, 130°C, closed vessel, 30 min [6].

Table 1. Optimization of conditions for the Chan-Evans-Lam cross-coupling reaction.

Reaction		Conditions	Time	Yield	Ref.
d	i	$Cu(OAc)_2$, Et_3N, DCE (5mL), stirring, rt, open vessel	72 h	NR	[4]
	ii	$Cu(OAc)_2$, Et_3N, MeCN (3mL), stirring, rt, O_2	24 h	37%	[5]
	iii	$Cu(OAc)_2$, Et_3N, MeCN (3mL), US, rt, O_2	1,5 h	56%	NA
	iv	$Cu(OAc)_2$, Et_3N, MeCN (3mL), US, rt, O_2 (doubling concentration)	1,5 h	82%	NA
	v	$Cu(OAc)_2$, Et_3N, MeCN (6mL), US, rt, O_2 (doubling quantities)	1,5 h	89%	NA

Figure 2. Highlights of the synthesis.

RESULTS - ^{1}H-NMR SPECTRA

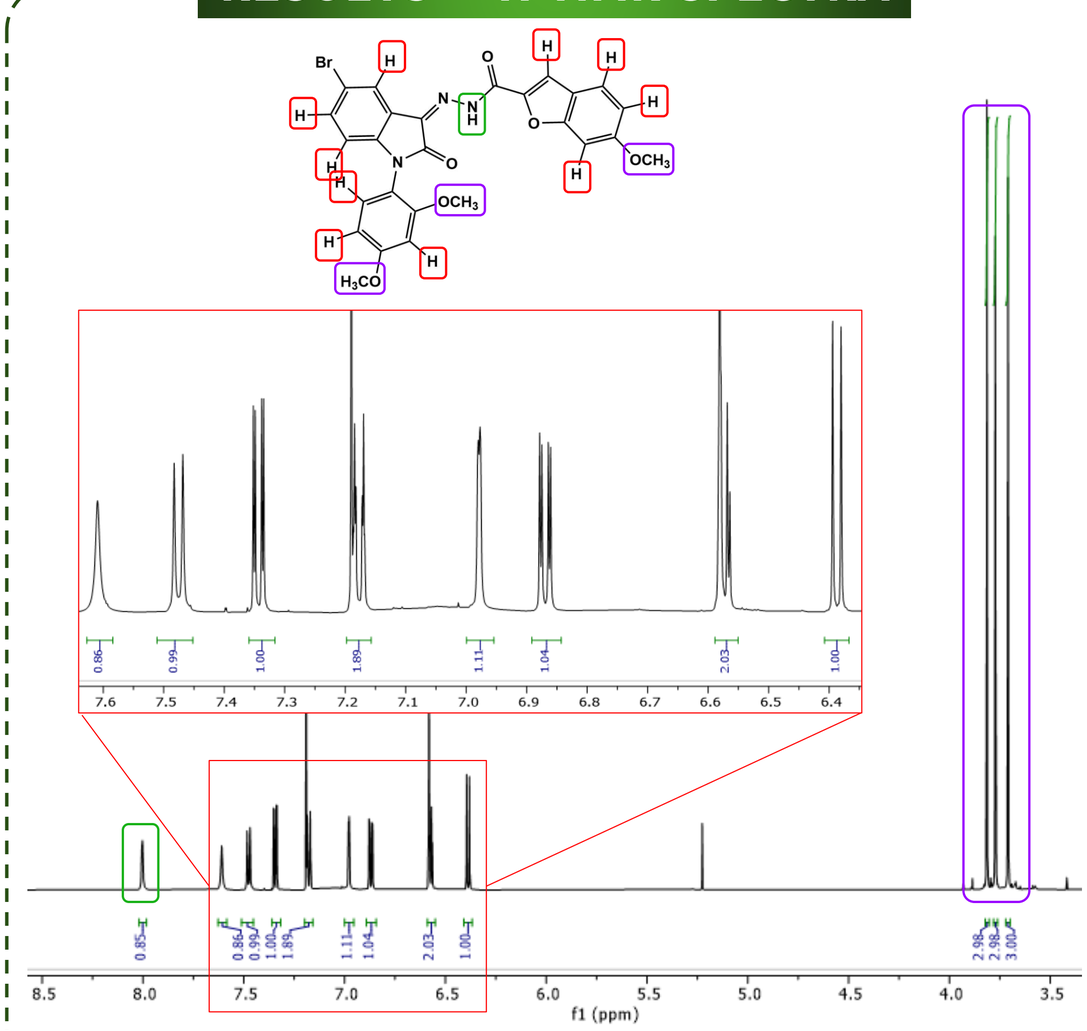


Figure 3. ^{1}H-NMR spectrum for the 2,4-dimethoxy substituted derivative.

CONCLUSIONS

1. Six of the proposed isatin-benzofuran conjugated hybrid derivatives have been successfully synthesized.

1. The coupling reaction for the *N*-arylation of 5-bromoisatin was optimized for short reaction time and high yield, due to the use of ultrasound and scaling of the reaction without changing the concentration of the reactant species.

1. The different stages involve simple synthesis protocols with high yields, easy purification procedures and complies with several principles of green chemistry. The final product obtained is confirmed by ^{1}H-NMR.

REFERENCES

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