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PROMISING ANTITUMOR AGENTS: SYNTHESIS AND CYTOTOXITY OF NEW *O*-DODECYL-SUBSTITUTED ARYLMETHYLIDENE THIAZOLO[3,2-*A*]PYRIMIDINES

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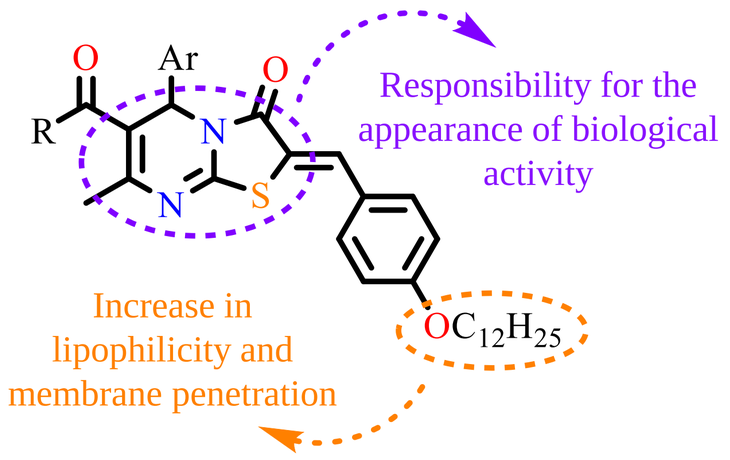
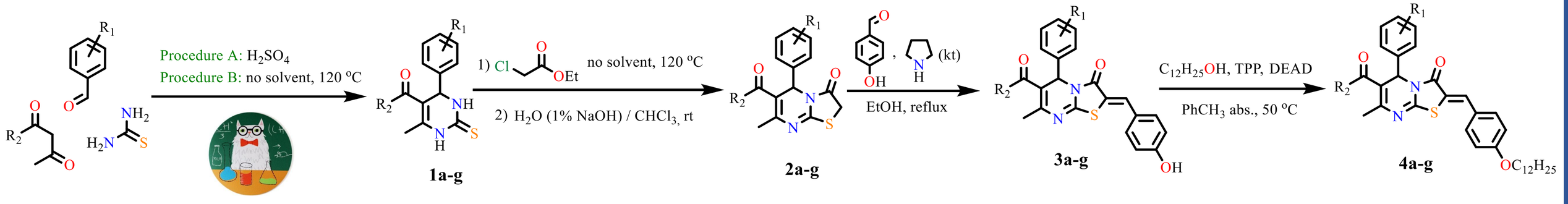
PROBLEM STATEMENT AND RELEVANCE

Heterocyclic compounds containing the thiazolo[3,2-*a*]pyrimidine scaffold are of significant interest in medicinal chemistry due to their broad spectrum of biological activities. In recent years, this heterocyclic fragment has been shown to serve as a key structural unit for the development of new pharmacophores exhibiting antimicrobial, antibacterial, and anti-inflammatory properties. One effective strategy for modifying such molecules to improve their drug-like properties is the introduction of lipophilic fragments. The addition of a long-chain alkyl substituent, such as an *n*-dodecyl group, can significantly increase the compound's lipophilicity. This, in turn, facilitates better penetration through cellular membranes and enhances bioavailability, potentially amplifying the therapeutic effect.

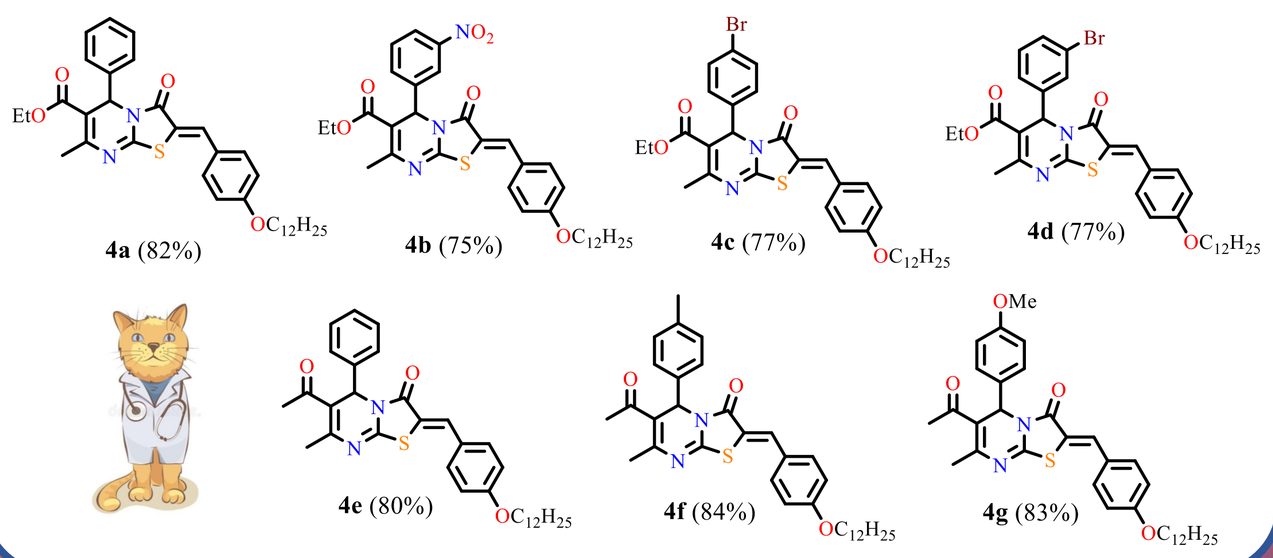


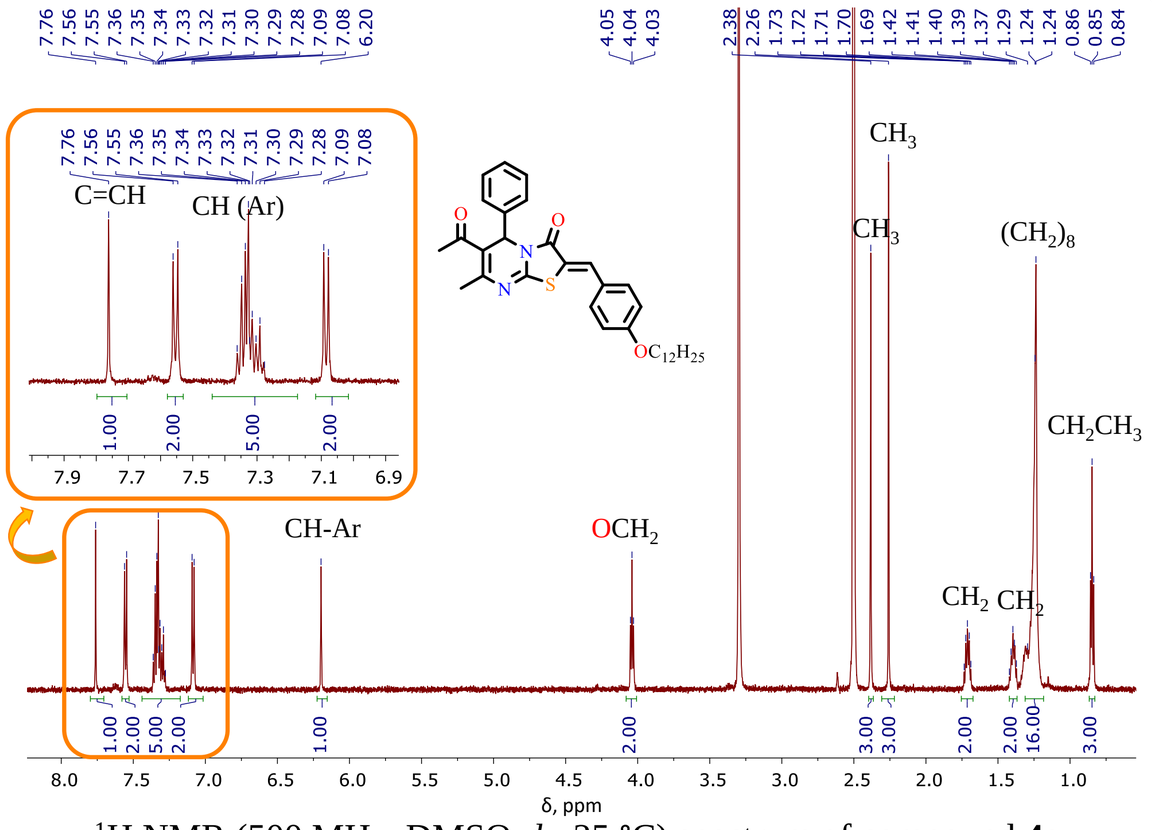
GENERAL SYNTHESIS OF TARGET COMPOUNDS



The four step synthetic route, consisting of 1) Biginelli-type reaction; 2) Ring-closing condensation; 3) Knoevenagel condensation; 4) Mitsunobu reaction

THE SCOPE OF DODECYLOXYBENZYLIDENE DERIVATIVES OF THIAZOLO[3,2-*A*]PYRIMIDINES





^{1}H NMR (500 MHz, DMSO-d_6, 25 °C) spectrum of compound **4e**

Test Compounds	IC_{50} (μM)					
	Cancer cell lines					Normal cell lines
	M-HeLa	MCF-7	PC3	HuTu 80	T98G	Wi38
4a	93.3±3.0	>100	93.5±6.3	63.5±5.7	60.5±4.2	292±23
4b	>100	>100	**45.1±3.2** *SI-8*	**60±6.0** *SI-5.7*	**61.4±4.3** *SI-5.6*	342±27
4c	>100	>100	73.6±5.9	86.7±6.6	80.4±5.6	98.2±7.9
4d	>100	>100	58.0±3.5	95.4±6.9	84.5±5.7	136.3±10
4e	>100	68.4±4.1	98.0±7.1	**19.7±1.4** *SI-4.5*	85.3±6.1	88.4±6.9
4f	>100	67.4±4.3	**95.0±6.8** *SI-2.4*	**54.0±5.0** *SI-4.2*	**55.4±3.9** *SI-4.1*	229±18
4g	>100	>100	92.0±6.4	**23.1±1.6** *SI-4.7*	**30.7±2.1** *SI-3.5*	109.1±8.0
Sorafenib	25.0±1.8	27.5±2.2	12.7±1.1	5.0±0.4	12.9±0.8	21.7±1.7

CONCLUSION

1) The structure and high purity of all synthesized intermediate and final compounds were unambiguously confirmed by a comprehensive set of physicochemical analysis methods
2) The synthesized compounds were subjected to *in vitro* screening for antitumor activity against a panel of cancer cell lines. The obtained compounds exhibited moderate, yet statistically significant, cytotoxic activity against all tested cell lines. However, it is worth noting that the obtained derivatives did not show cytotoxic effects on normal cells, and therefore have a high selectivity index for cancer cell lines.
3) It was demonstrated that the insertion of the *n*-dodecyl fragment indeed led to the emergence of biological activity. The observed effect suggests that the strategy of increasing molecular lipophilicity is justified for this class of compounds. The moderate activity provides a promising starting point for further structural optimization aimed at creating more potent and selective antitumor agents.

M-HeLa (a cervical cancer cell line), MCF-7 (a breast cancer cell line), PC3 (a prostate cancer cell line), HuTu 80 (an adherent cell line), T98G (a glioblastoma cell line), Wi38 (a diploid human cell line), *Sorafenib* (comparison drug), SI (selectivity index)