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Synthesis and anticancer screening studıes of indole-based piperazıne derivatives

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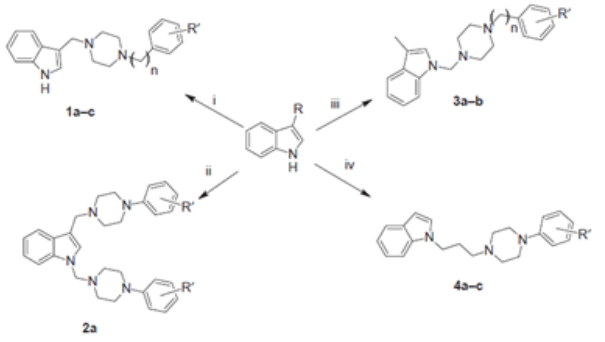
The preparation of the compounds is illustrated in Scheme 1 . The groups of 3-{[4-(substituted phenyl/benzyl)piperazin-1-yl]methyl}-1H-indole 1a-ca, 1,3-di-{[4-(4-fluorophenyl)piperazin-1-yl]methyl}-1H-indole 2a and 1-{[4-(substituted phenyl / phenylethyl)piperazin-1-yl]methyl}-3-methyl-1H-indole 3a-b were prepared by Mannich reaction of substituted piperazine and formaldehyde with indole or 3-methylindole. The crude products were purified by recrystallization or column chromatography. 1-{3-[4-(substitutedphenyl)piperazin-1-yl]propyl}-1H-indole 4a-c were synthesized by the reaction of indole and 1-(3-chloropropyl)-4-(substituted phenyl) piperazine in presence of potassium hydroxide. To obtain 1-(3-chloropropyl)-4-(substitutedphenyl) piperazine, substituted phenyl piperazine was reacted with 1-bromo-3-chloropropane. Compounds 4a-c were purified by column chromatography on silica gel using ethyl acetate/n-hexane as a mobile phase system (Scheme 1). Structures of compounds were clarified with IR, ^{1}H-NMR, ^{13}C-NMR, mass spectroscopies and elemental analyses.



	1a	1b	1c	2a	3a	3b	4a	4b	4c
R	H	H	H	H	CH_3	CH_3	H	H	H
n	0	1	1	-	0	2	-	-	-
R′	4-F	2,5-diF	3,4-diCl	4-F	4-F	H	4-F	2-F	H

Scheme 1: Synthesis of compounds **1a–c**, **2a**, **3a–b**, and **4a–c**. Reagent and conditions: (i) HCHO, substituted piperazine, EtOH, room temperature; (ii) HCHO, 4-F-phenylpiperazine, EtOH, reflux, 4 h; (iii) HCHO, substituted piperazine, EtOH, reflux, 4 h; and (iv) 87% KOH, DMSO, room temperature, 1 h; 1-(3-chloropropyl)-4-(substitutedphenyl)piperazine, DMSO, 0 °C, 20h.

The cytotoxic activity of the synthesized compounds was investigated on liver (HUH7), breast (MCF7), and colon (HCT116) cancer cell lines, by means of sulphorhodamine B (SRB) assays in triplicate. Among compounds, the best inhibitory activity against HUH7 (IC50=3.42 lM) was exhibited by compound 1c (3-{[4-(3,4-dichlorobenzyl)piperazin-1-yl]methyl}-1H-indole).

Biography

Mine Yarim has studied anticancer drug design for 20+ years, during which time she has authored several peer-reviewed reports. She has served on numerous review committees for the National Science Foundation in Turkey.

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