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Synthesis, spectroscopic structure identification, X-ray study and anticancer activities of new angularly fused quinobenzothiazines

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ABSTRACT

Synthesis of 16 new tetracyclic angularly fused azaphenothiazines, 8-, 9- and 10-substituted quinobenzo-1,4-thiazines (benzo[a]-3-azaphenothiazines) was based on the reactions of dichlorodiquinolinyl disulfide and diquinodithiin with substituted anilines. Whereas the reactions with *p*-fluoroaniline and *p*-methylthioaniline led to only one product, the reaction with *m*-triflouromethylaniline led to isomeric compounds. The obtained 8-10-substituted 12*H*-quinobenzothiazines were further transformed into 12-substituted derivatives through alkylation of the thiazine nitrogen atom. The structure analysis was based on 1D and 2D NMR (NOESY, COSY, HSQC and HMBC) spectra which enabled to distinguish the isomers and to exclude retro-Smiles rearrangement and the azine nitrogen atom alkylation pathways. This supposition was fully confirmed by X-ray analysis showing the quinobenzothiazine system to be folded and the substituent at the thiazine nitrogen atom in an equatorial position. Some compounds exhibited anticancer activity against MCF-7, MDA-MB-231 and SNB-19 cell lines similar to a reference drug cisplatin. The structure-activity relationship of the compounds were discussed.

1. Introduction

Cancer has been still recognized as one of the main health problems which causes mortality and morbidity worldwide for the last many years. The anticancer therapy involves surgery, radiation, chemotherapy and biotherapy as curative treatments [1,2]. Although chemotherapy has been widely used and still improved, and survival greatly has been increased, there is an urgent need to find new potent antitumor agents possessing different mechanisms of action with better selectivity and fewer side effects. In recent years, compounds with heterocyclic ring system play an important role for the development of novel chemotherapeutic scaffold with improved pharmaceutical properties [3,4].

Tricyclic fused heterocyclic compounds of the dibenzo-1,4-thiazine structure have been known as phenothiazines possessing important biological actions and interesting chemical properties. Their 10-dialkylaminoalkyl derivatives with an additional simple substituent in position 2 have been highly recognized drugs exhibiting neuroleptic, antihistaminic, antitussive and antiemetic activities [5]. Those classical phenothiazines are compounds of low toxicity, inexpensive, easy to obtain, and their substrates, 10*H*-dibenzothiazines, are even commercially available. The chemical modifications of the phenothiazine structures have been carried out mainly by introduction of new substituents at the thiazine nitrogen atom and by replacement of one or two benzene rings with the homoaromatic and heteroaromatic rings to form benzophenothiazines and azaphenothiazines (azinobenzothiazines and diazinothiazines). Such modifications are directed to alter biological properties (potency and activity). Both classical and modified phenothiazines are reported in the last decade to exhibit very promising anticancer, antibacterial, antifungal, anti-inflammatory activities, reversal of multidrug resistance and many other actions. This abundant experimental material reported in hundreds articles was summarized recently in review articles and chapters in monographs [6–15].

The phenothiazine structure modification with the azine ring is

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