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## A novel piperazine linked $\beta$ -amino alcohols bearing a benzosuberone scaffolds as anti-proliferative agents

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### ABSTRACT

A new series of 1-((9-chloro-2, 3-dimethyl-6, 7-dihydro-5H-benzo [7] annulen-8-yl)methoxy)-3-(4-phenylpiperazin-1-yl) propan-2-ols (**6a-k**) have been designed, synthesized and their structures were established by spectroscopic data (FT-IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, HRMS) and further confirmed by X-ray analysis. The newly synthesized compounds **6a-k** were evaluated for their *in vitro* anti-proliferative activity against four cancer cell lines such as HeLa (cervical), MDA-MB-231 (breast), A549 (lung) and MIAPACA (pancreatic). Among the compounds tested, the compound **6e** displayed most potent activity against four cancer cell lines with GI<sub>50</sub> values ranging from 0.010 to 0.097  $\mu$ M. The structure and anti-proliferative activity relationship was further supported by *in silico* molecular docking study of the active compounds against Colchicine binding site of  $\beta$ -tubulin.

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Cancer is one of the most common diseases worldwide; it is the second-leading cause of deaths in the world. The identification of new therapies is an area of ongoing importance in biomedical research.<sup>1-2</sup> Cervical, breast, lung, colon, and pancreatic cancers are most common in the developing and under developed countries. Therefore, the development of new anticancer agents and more selective treatment strategies for cancer has received more and more attention for medicinal chemists.

Natural products containing seven membered ring fused to an aromatic ring attracted considerable attention in recent years due to their remarkable biological activities. Benzocycloheptenone and its derivatives are an important class of heterocyclic compounds, which constitute the key core of various natural products and play a unique role in drug discovery program. The benzosuberone moiety is the main scaffold of several natural products. For example, Theaflavin<sup>3</sup> present in black tea and Colchicine<sup>4</sup> from the plant *Colchicum autumnale* are two natural alkaloids with potent anti-cancer activity (**Fig. 1**). On the other hand  $\beta$ -amino alcohol fragment is a common structural subunit in natural products and plays a key role in medicinal chemistry, pharmaceuticals and in organic synthesis.<sup>5-6</sup>

Many  $\beta$ -amino alcohols exhibit a broad spectrum of biological activities.<sup>7</sup> These molecules are usually prepared from aminolysis of epoxide and are non volatile, completely odorless products.  $\beta$ -amino alcohols Hapalosin, Swainsonine are found as potential anticancer agents (**Fig. 1**).<sup>8-11</sup> Piperazine based  $\beta$ -amino alcohols are known for their biological activity. They find application as positive inotropic agents, increasing myocardial contractility, in the treatment of cardiac disorders such as congestive heart failure.<sup>12-15</sup> Some of the  $\beta$ -amino alcohols bearing the piperazine motif (MS-073 and MS-209) (**Fig. 1**) are found to have application in the reversal of multidrug resistance in cancer cells.<sup>16</sup>

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