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Synthesis and antiproliferative activity of novel polynuclear heterocyclic compounds derived from 2,3-diaminophenazine

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ABSTRACT

2,3-Diaminophenazine **1** was used as a precursor for the preparation of some novel phenazine derivatives such as imidazo[4,5-*b*]phenazine-2-thione **2**, its methylthio **3**, ethyl 1-aryl-3*H*-[1,2,4]triazolo [2,3-*a*]imidazo[4,5-*b*]phenazines **8a–c**, ethyl (2*Z*)-[3-aminophenazin-2-yl)amino](phenylhydrazono) ethanoate **9**, pyrazino[2,3-*b*]phenazine derivatives **10**, **12**, **15–17**, [1,4]diazepino[2,3-*b*]phenazine derivatives **13**, **14**, 2,3-dibenzoylaminophenazine **18,** 1*H*-Imidazo[4,5-*b*]phenazine derivatives **20**, **23a–c**, **24**, **25** and 4-[(*E*)-(3-amino phenazin-2-yl)diazenyl] derivatives **27–29**. All compounds were tested as inhibitors of the proliferation of human lung carcinoma and colorectal cancer cell lines through inhibition of Tyrosine Kinases. Most of compounds exert good activity against the two cancer cell lines. Five compounds (**1**, **2**, **3**, **25** and **28**) were found to possess the same activity as the standard drug Cisplatin.
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1. Introduction

It was reported that some phenazine derivatives demonstrated significant antimicrobial [1], antimycobacterial [2], antifungal activity [3–5], and are used in a large scale as anticancer [6], anthelmintic [7–9], antibiotic drugs [10,11]. On the other hand, they have potential therapeutic antitumor application [12], act as chemopreventive agent [13] and they recorded a great ability of reduction in blood and urine glucose level [14]. Conventional chemotherapy, although directed toward certain macromolecules or enzymes, typically does not discriminate effectively between rapidly dividing normal cells (e.g., bone marrow and gastrointestinal tract) and tumor cells, thus leading to several toxic side effects. Tumor responses from cytotoxic chemotherapy are usually partial, brief, and unpredictable. In contrast, targeted therapies interfere with molecular targets that have a role in tumor growth or progression. These targets are usually located in tumor cells, although some like the antiangiogenic agents may target other cells such as endothelial cells [15]. Thus, targeted therapies have a high specificity toward tumor cells, providing a broader therapeutic window with less toxicity. They are also often useful in combination with cytotoxic chemotherapy or radiation to produce additive or synergistic anticancer activity because their toxicity profiles often do not overlap with traditional cytotoxic chemotherapy. Thus, targeted therapies represent a new and promising approach to cancer therapy, one that is already leading to beneficial clinical effects. There are multiple types of targeted therapies available, including monoclonal antibodies, inhibitors of Tyrosine Kinases and antisense inhibitors of growth factor receptors [15].

Protein kinases (PKs) are indispensable for numerous processes in the cell. Tyrosine Kinases are important mediators of signal transduction process, leading to cell proliferation, differentiation, migration, metabolism and programmed cell death (apoptosis) [16]. These enzymes catalyze phosphorylation of different cellular substrates. Phosphorylation in turn regulates various cellular functions. Normally, their activity is stringently regulated. However, under pathological conditions PKs can be deregulated, leading to alterations in the phosphorylation and resulting in uncontrolled cell division, inhibition of apoptosis, and other abnormalities and consequently to diseases [17]. Various cancers and other diseases are known to be caused or accompanied by deregulation of the phosphorylation. Inhibition of PKs has been shown to be a

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promising therapeutic strategy for cancer. In view of the above mentioned findings and as continuation of our efforts [18–20] in designing new potent, selective and less toxic biologically active compounds, we would like to report here simple convenient methods for the synthesis of some phenazine incorporating different heterocycles to evaluate them as inhibitors of the proliferation of the human lung carcinoma A549 and colorectal cancer HCT116 cell lines through inhibition of human TRK activity.

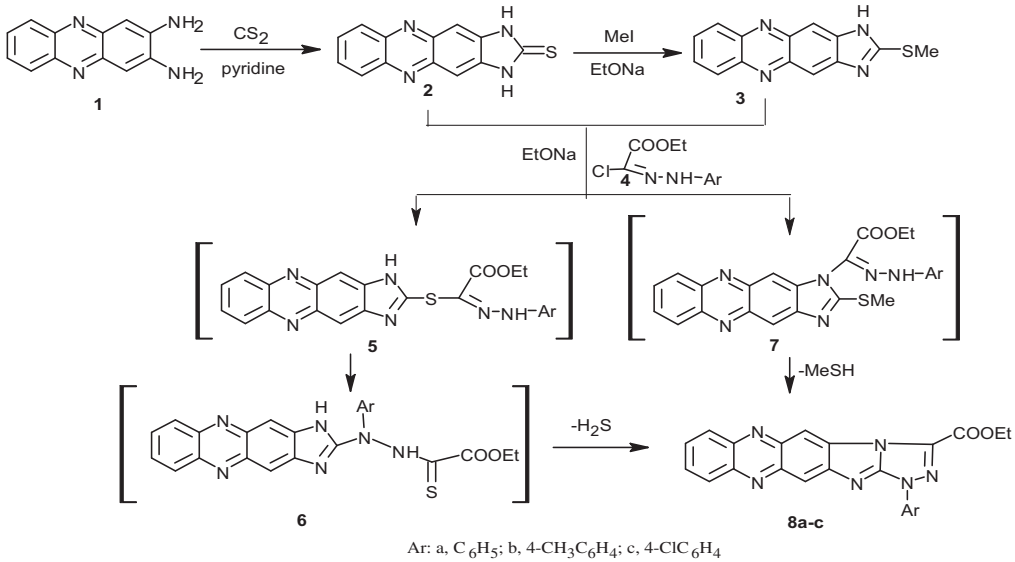
2. Results and discussion

2.1. Chemistry

The required starting 2,3-diaminophenazine **1** was prepared as previously reported procedure [21]. Refluxing compound **1** with carbon disulfide in pyridine afforded imidazo[4,5-*b*]phenazine-2-thione **2**. The structures of the latter product were based on microanalytical and spectroscopic data. The IR spectrum showed two absorption bands at 3495, 1425 cm^{-1} due to NH, and C=S group respectively. The mass spectrum reveled a molecular ion peak at *m*/*z* (%) 252 (M^+, 100) corresponding to $C_{13}H_8N_4S$. Treatment of **2** with methyl iodide in the presence of sodium ethoxide in refluxing ethanol afforded 2-methylsulfanyl-imidazo[4,5-*b*]phenazine **3**. The structure of **3** was established on the bases of its elemental analysis and spectral data. The mass spectrum showed a molecular ion peak at *m*/*z* (%) 266 (M^+, 100) corresponding to $C_{14}H_{10}N_4S$. While its ^1H NMR revealed the presence of singlet signal at δ 2.47 ppm characteristic of the S–**CH_3** protons (c.f. Experimental, Scheme 1). The reaction of **2** with ethyl N^1-phenylhydrazon-N^2-chloroacetate **4a–c** [22] in ethanol in the presence of sodium ethoxide under reflux, gave in each case after work up only isolable products **8a–c**. The structures of the latter products **8a–c** were confirmed on the basis of microanalytical and spectral data. The mass spectrum of **8a** as an example showed a molecular ion peak at *m*/*z* 408 (M^+) corresponding to formula $C_{23}H_{16}N_6O_2$. Its IR spectrum showed absorption band at 1727 characteristic of C=O (ester), while its ^1H NMR revealed the presence of a triplet signal at δ 1.38–1.41 ppm and quartet signal at δ 4.50–4.55 ppm characteristic of the ethyl ester protons. To account for the formation of **8** from reaction of **1** with **4**, the step reaction mechanism outlined in (Scheme 1) is suggested. The reaction involves an initial formation of thiohydrazonate ester **5** via nucleophilic substitution of chloride in **4**. The formed thiohydrazonate **5** undergoes *in situ* Smiles rearrangement [23–26] under the reaction conditions employed, to give the thiohydrazide intermediate **6**, which in turn undergoes cyclization with concurrent loss of hydrogen sulfide to give the respective **8a–c** (Scheme 1) The assignment of the formation of **8a–c** was further supported by alternative synthesis of **8**. Thus, treatment of 2-methylthio derivative **3** with **4** in ethanol in the presence of sodium ethoxide under reflux led to the formation of products that proved to be identical in all respects (m.p., mixed m.p. and IR) with compound **8**. Evidently, the mechanism proposed for the reaction of **3** with **4** proceeds through two steps, the first step involves acylation of **3** with **4** to give amidrazone derivative intermediate **7**, which in turn undergoes *in situ* cyclization with concurrent elimination of methanthiol to give **8a–c** as end products (Scheme 1).

Treatment of equimolar quantities of **1** and ethyl N^1-phenylhydrazon-N^2-chloroacetate **4** in ethanol/DMF mixture at reflux temperature in the presence of triethylamine afforded a new compound, namely ethyl (2*Z*)-[3-(aminophenazin-2-yl)amino]-(phenylhydrazono)ethanoate **9**. The mass spectrum of **9** showed a molecular ion peak at *m*/*z* 400 (M^+) corresponding to molecular formula $C_{22}H_{20}N_6O_2$. Its IR spectrum showed absorption bands at 3320 and 1720 cm^{-1} attributed to the presence of NH, CO ester, respectively. Treatment of **9** with acetic anhydride/acetic acid mixture at reflux afforded single product **10** or **11** as evidenced by TLC analysis. The mass spectral data and elemental analysis of this product are consistent with the structure **10** (Scheme 2). Also, the ^1H NMR spectrum does not contain the characteristic signals of the ethoxy group protons (c.f. Experimental, Scheme 2). Oxidation of **10** with hydrogen peroxide gave product whose mass spectrum showed a molecular ion peak at *m*/*z* 352 (M^+) corresponding to molecular formula $C_{20}H_{12}N_6O$. The IR spectrum showed absorption bands at 3411 (NH), 1680 (C=O), 1650 (N=N) corresponding to 2-oxo-3-phenylazo-1*H*-pyrazino[2,3-*b*]phenazine **12** (Scheme 2).

Refluxing equimolar quantities of **1** and ethyl acetoacetate in DMF gave one isolable product as evidenced by TLC analysis of the crude product. The mass spectral data and elemental analysis indicated a molecular formula $C_{16}H_{14}N_4O$. The IR spectrum showed bands at 3368, 3061 (2NH), 2977 (CH_3), 2927 (CH_2), and 1660 (C=O) corresponding to 6*H*-7-methyl[1,4]diazepino[2,3-*b*]phenazine-



Ar: a, C_6H_5; b, 4-$CH_3C_6H_4$; c, 4-ClC_6H_4

Scheme 1. Synthesis of compounds **2–3**, **8a–c**.

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