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Original article

One-pot synthesis of pyrazoline derivatised carbazoles as antitubercular, anticancer agents, their DNA cleavage and antioxidant activities

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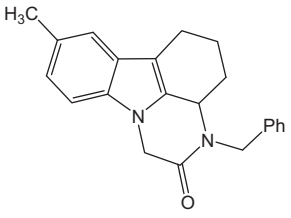
ABSTRACT

Novel tricyclic carbazoles **4a**–**k** were synthesized in one-pot employing sydnone derivatives **3a**–**k** as masked hydrazines by the ring transformation in presence of conc. HCl and cyclohexanone. The title compounds were screened for anti-tubercular, anti cancer, DNA cleavage, antioxidant activity. MIC, GI50, LC50, TGI were evaluated. The title compounds have exhibited significant antitubercular, DNA cleavage and antioxidant activities and partial anticancer activity.

1. Introduction

Sydnones, which are representatives of mesoionic heterocyclic compounds, possess a broad spectrum of pharmacological activities and have been used as synthons in 1,3-dipolar cycloadditions to be transformed to 1,3,4-oxadiazole, pyrazole, phenyl indazole, pyrazoline and tetrazine [1–5]. The tricyclic carbazole nucleus is an important structural unit existing in many natural alkaloids and synthetic derivatives possessing variant biological activities [6,7], especially those carbazoles fused with a heterocyclic fragment [8,9]. Tuberculosis (TB), a highly infectious disease primarily caused by *Mycobacterium tuberculosis*, is one of the oldest recorded human afflictions and remains today a leading cause of impoverishment, human suffering and death [10]. Carbazole derivatives *viz*., N-alkylated hexahydropyrazinocarbazole (**1**) and amino-tetrahydrocarbazole (**2**) reported to exhibit moderate *in vitro* activity against mycobacterium (human $H_{37}Rv$ type *M. tuberculosis*) [11].



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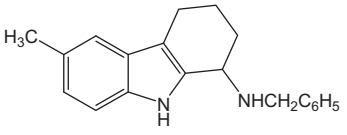

2

The numbers and types of compound that have been reported to show anticancer activity are legion and numerous new examples are constantly under investigation. It is well known that the utility of cancer chemotherapy is considerably restricted by toxic side effects of anticancer drugs. This restriction results from the fact that the anticancer drugs used in the present chemotherapy lack efficient selectivity for malignant cells. Adriamycin is one of the most powerful and widely used anticancer drugs [12]. The fused-ring carbazoles look more like classical intercalators than groove binding agents, but based on kinetic and spectroscopic, particularly NMR results, compounds bind in the minor groove in AT sequences despite their quite different and fused aromatic structures. A second initially surprising feature of the carbazole–DNA interactions is that the proposed interaction mode of the 3,6-substituted carbazole has the carbazole NH group pointed out of the DNA minor groove while

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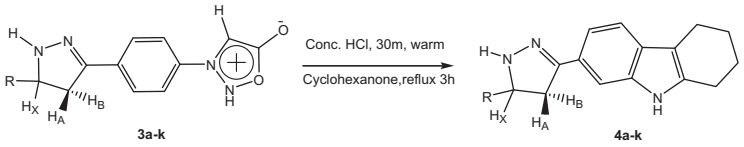


a; R = Phenyl, **b**; R = *o*-chlorophenyl, **c**; R = *m*-chlorophenyl, **d**; R = *p*-chlorophenyl, **e**; R = *p*-nitrophenyl, **f**; R = *o*-hydroxyphenyl, **g**; R = *p*-hydroxyphenyl, **h**; R = styryl, **i**; R = methyl, **j**; R = *p*-anisyl, **k**; R = *p*-tolyl

Scheme 1. Synthesis of title compounds **4a**–**k**.

with the 2,7-derivative the NH points into the groove and is directly involved in carbazole–DNA complex formation [13].

Research in recent years has shown the implication of oxidative and free-radical-mediated reactions in degenerative processes related to ageing [14,15] and in diseases *viz*., cancer, coronary heart disease, and Alzheimer's disease [16,17]. Antioxidant defenses in the organism against reactive oxygen species (pro-oxidants and free radicals) produced during normal cell aerobic respiration may be of endogenous (enzymatic and non-enzymatic) or dietary origin (vitamins, carotenoids, flavonoids, etc.) [18,19].

Many studies have been focused on the design of analogues of carbazoles which possess anti tubercular, anticancer, DNA cleavage ability of pathogens and also which act as anti-oxidants. Owing to these observations and our zeal to explore newer carbazole molecules, we herein report the synthesis and *in vitro* evaluations, for the new carbazole compounds derivatised from 3-[4-(5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)]-phenylsydnones **3a**–**k**. Synthesis of substituted carbazoles may be achieved efficiently by ring transformation of sydnone ring which acts as masked hydrazine. Through Fischer- Indole synthesis an easy mode of preparation of these compounds can be achieved with lesser reaction times and easier workup procedures in excellent yields which add on to the advantages of addition of newer molecules to the library of compounds.

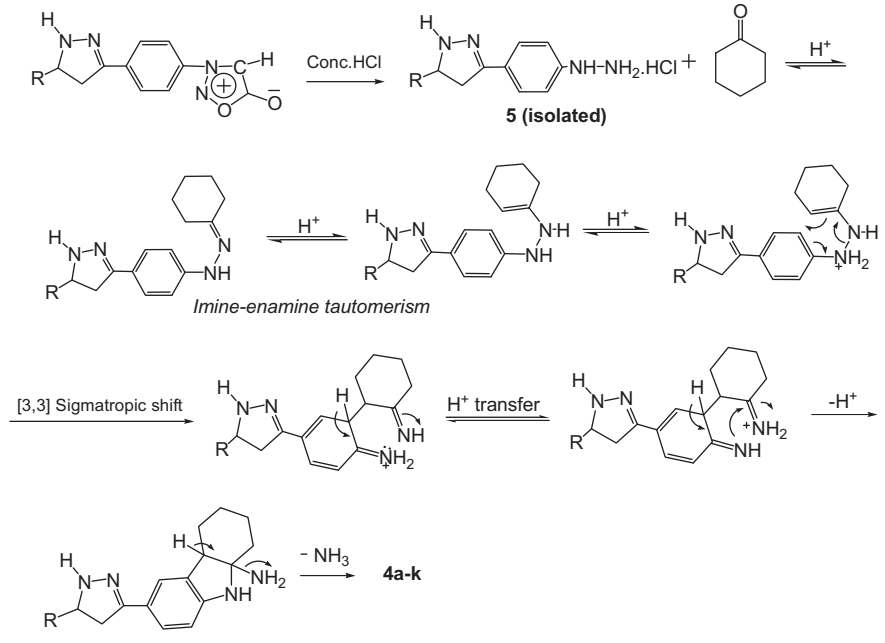
2. Chemistry

The general synthetic strategy employed to obtain the title compounds is depicted in Scheme 1. The sydnone ring cleavage of 3-[4-(5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)]phenylsydnone **3a**–**k** in conc. HCl and absolute alcohol at around 75–80 °C followed by cyclization by the addition of cyclohexanone and refluxing the contents at 150 °C for 3 h led to the formation of 6,7,8,9-tetrahydro-2-(4,5-dihydro-5-aryl-1*H*-pyrazol-3-yl)-5*H*-carbazole **4a**–**k**. This eco-friendly method for the preparation of carbazoles is particularly attractive because it specifically generates pure amorphous products. All the newly synthesized compounds were characterized using IR, ^{1}H NMR, ^{13}C NMR, GCMS and elemental analysis.

3. Results and discussions

3.1. Chemistry

The synthetic strategy involved the reaction of various aryl pyrazoline sydnones with conc. HCl in absolute alcohol at 75–80 °C to cleave the sydnone ring followed by the addition of cyclohexanone and refluxing the contents at 150 °C to form carbazole ring. Maintenance of the above mentioned temperatures respectively was essential for cleavage and reconstruction of the ring. The probable mechanism for the ring transformation of sydnone into



Scheme 2. Proposed mechanism for the formation of title compounds **4a**–**k**.