Synthesis and Biological Evaluation of Some Isatin-based Mannich Bases

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ABSTRACT
In this study, a series of isatin-based Mannich bases were prepared and their biological activity was evaluated. Schiff bases of isatin were synthesized by condensation of the keto group of isatin with different aromatic primary amines. The N-Mannich bases of the above Schiff bases were synthesized by reaction of the acidic imino group of isatin with formaldehyde and secondary amine. The chemical structures of the title compounds have been confirmed and elucidated by means of their physical and spectral data respectively. The compounds were tested for their possible antibacterial, analgesic and anti-inflammatory activities by the standard methods. Among the tested compounds, the compound containing the chloro group showed significant biological activity. These pilot studies demonstrate the usefulness of isatin-based Mannich bases.

KEYWORDS: Isatin; Antibacterial; Analgesic; Anti-inflammatory.

Introduction
Isatin is an endogenous compound isolated in 1988 (Glover et al., 1988) and reported to possess a wide range of biological activities. It is an endogenous indole found in the mammalian brain, peripheral tissues and body fluids (Medvedev et al., 2005). Schiff and Mannich bases of isatin represent one of the important classes of organic compounds because of their broad spectrum of pharmacological activities such as antibacterial (Chhajed et al., 2010; Ramesh et al., 2001), antifungal (Pandeya et al., 1998; Singh et al., 2010), antiviral (Aliasghar et al., 2007; Sriram et al., 2005), anti-HIV (Bal et al., 2005; Pandeya et al., 1999), anti-inflammatory (Ramesh et al., 2001), analgesic (Khan et al., 2006) and anticonvulsant (Varma et al., 2004; Khan et al., 2006) activities.

In the present study, aromatic primary amines were subjected to reaction with isatin to form the Schiff bases. The corresponding N-Mannich bases were synthesized by reacting them with the secondary amine and formaldehyde. The chemical structures of the synthesized compounds were confirmed by means of their physical, IR, 1H-NMR and Elemental data. The synthesized compounds were tested for their antibacterial activity by the cup plate method, analgesic activity by acetic acid induced writhing response, hot plate reaction time, tail immersion method, and anti-inflammatory activity by carrageenan-induced paw edema method.

Materials and Methods Chemistry
Melting points were determined by the open-ended capillary tube on Veego electrical melting point apparatus, expressed in °C and are uncorrected. The IR spectra of the compounds were recorded on Shimadzu IR Affinity series-1 in KBr and the values were expressed in cm⁻¹. The 1H-NMR spectra of the compounds were recorded on a Bruker Advance II 400 MHz spectrophotometer and the values were expressed in δ ppm. Elemental analysis was performed in a Carlo Erba 1108 elemental analyzer. The purity of the compounds was checked by thin layer chromatography on silica gel G coated plates.

Procedure for synthesis of Schiff bases of isatin
Equimolar (0.01 mol) quantity of isatin and substituted anilines were dissolved in a sufficient amount of ethanol and refluxed for 3 h in presence of glacial acetic acid. After standing for approximately 24 h at room temperature, the products were separated by filtration, dried under vacuum and recrystallized from warm ethanol.

Procedure for synthesis of Mannich bases of isatin
An equimolar quantity of morpholine (0.004 mol) in 10 ml of ethanol was added to a slurry containing appropriate isatin and formaldehyde solution (37% v/v) in 10 ml of ethanol. The reaction mixture was stirred for 2 h at room temperature and kept under refrigeration for 24 h. The product was separated by suction filtration, dried under vacuum and recrystallized from warm ethanol. The molecular formula, molecular weight, melting point, yield, elemental analysis, Rf and spectral data were presented in table-1 and 2. TLC was monitored by using solvent system benzene: chloroform (55:45) and the spots were identified by placing the dried plate in iodine chamber.