AMINOMETHYLATION OF 1,2,4-TRIAZOLE-3-THIONES CONTAINING PIPERIDINE MOIETY IN ORDER TO SYNTHESIZE NEW BIOLOGYCALLY ACTIVE COMPOUNDS

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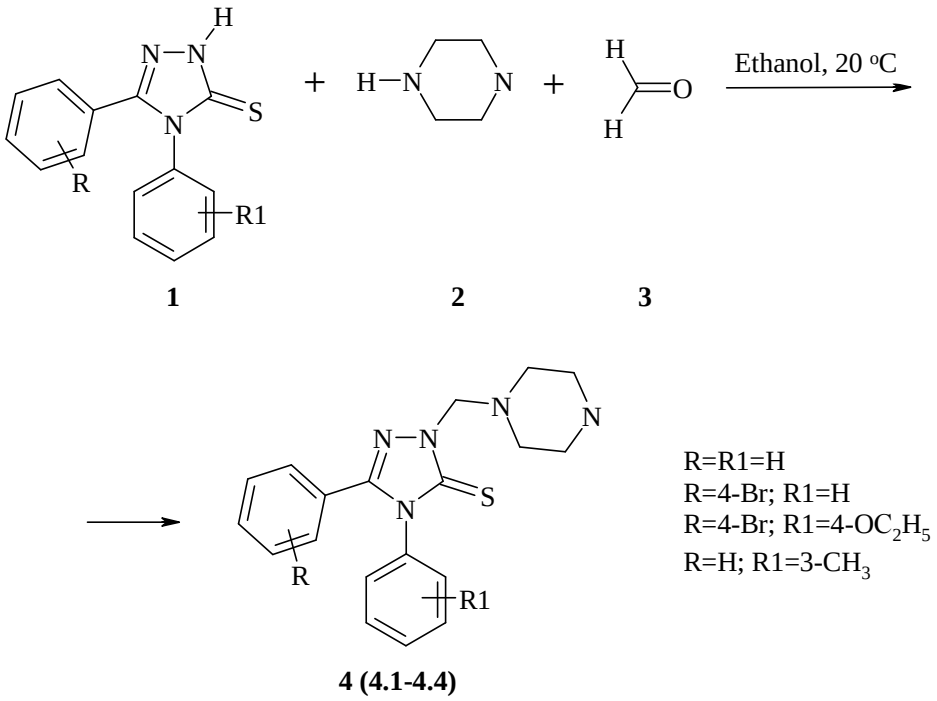
Introduction. Effective pain management has always been the deliberating task for scientists. Two major classes of traditional analgesics including nonsteroidal anti-inflammatory drugs and opioids are mainly used in treatment of pain [3]. Studies revealed that the analgesic potential of narcotic drugs is closely and strongly associated with binding of G-protein coupled opioid receptors in central nervous system, especially mu-opioid receptors. Reported adverse effects mainly; addiction, tolerance, dependence and abuse potential limited the clinical use of opioid drugs. Herefore, scientists focused on finding novel compounds having effective analgesic potential with limited side effects. In this regard many derivatives of morphine were developed to enhance therapeutic potential and lessen side effects by slight modification. Those derivatives exhibiting better activity than morphine. Structural activity relationship of morphine derivatives revealed that the presence of piperidine ring is necessary for analgesic activity.

Piperidine possesses enormous biological and pharmacological potential and presence of piperidine ring in various clinically used drugs reflects its importance in drug design. Pethidine, fantanyl, ohmefentanyl, remifentanyl, ketobemidon and a variety of molecules contain piperidine nucleus and used as effective analgesics. Extensive research presented that the substituted piperidine molecule showed potential therapeutic properties, good receptor binding and revealed as a leading nucleus with potent pharmacological actions therefore, widely used for the management of pain and inflammation. Recently, series of piperidine derivatives have been reported showing significant antinociceptive activity [5]. Various novel substituted piperidines have been prepared in our lab and most of the derivatives displayed potent analgesic activity.

Few Mannich bases derived from 1,2,4-triazoles carrying N-methylpiperazine substituent were biologically active [2]. In view of these facts and as continuation of our research on pharmaceutically important heterocycles [1, 4], hereby we report the synthesis of a new series of Mannich bases containing both 1,2,4-triazoles and piperidine skeletons.

Materials and methods. The series of 1,2,4-triazole-3-thione derivatives containing piperidine moiety ***4.1-4.4*** have been obtained in a one-pot multicomponent Mannich reaction involving 1,2,4-triazole-3-thiones, formaldehyde and secondary amine – piperidine in ethanol medium in accordance to the Scheme 1:

Results and discussion. The reaction proceeds via the formation of imminium ion which subsequently attacks the N-1 of triazole giving rise to regioselective Mannich base. It is interesting to note that the reaction is highly regioselective and furnishes only N-Mannich base and none of the S-Mannich derivatives, though the intermediate Schiff base can exist in the thiol–thione tautomeric equilibrium.



1 **2** **3**

4 (4.1-4.4)

Scheme 1

The yield of compounds obtained was 70-76 %.

Target compounds are white and light yellow crystalline substances with clear melting temperatures, soluble in organic solvents and insoluble in water.

Reaction is regioselective. Structure and purity of compounds have been established by means of ^{1}H NMR, ^{13}C NMR-spectroscopy, TLC and elemental analysis.

Conclusions. In order to synthesize new biologycally active compounds new series of 1,2,4-triazole-3-thione derivatives containing piperidine moiety have been obtained by Mannich reaction. Physico-chemical properties of the substances obtained have been studied.

References

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