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SYNTHESIS OF 1,3,4-OXADIAZOLES AND 1,3,4-THIADIAZOLES FROM ADIPIC ACID

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Annotation : Currently, there is a growing interest in biologically active heterocyclic compounds. In particular, dicarboxylic acids are widely used in the pharmaceutical industry as antibacterial, antifungal, and anti-inflammatory agents. Among dicarboxylic acids, adipic acid is considered one of the most important and industrially significant compounds.

In this study, the reactions of adipic acid with semicarbazide and thiosemicarbazide were investigated, leading to the formation of 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives, respectively. It was established that this process proceeds via the formation of hydrazides followed by intramolecular cyclization.

As a result, bis-heterocyclic compounds based on adipic acid were synthesized, which exhibit high biological activity and are considered promising candidates for the development of new therapeutic agents.

Keywords: adipic acid, semicarbazide, thiosemicarbazide, $POCl_3$, NH, 2-amino-1,3,4-oxadiazole, 1,3,4-thiadiazole.

Introduction: Five-membered heterocycles are widely represented among compounds used in clinical practice. Compounds containing pyrrole, oxazole, and thiazole scaffolds, together with their derivatives, are particularly important. Among these, 1,3,4-oxadiazoles and 1,3,4-thiadiazoles occupy a prominent position. Their diverse pharmacological activities have attracted increasing attention from researchers (Lata S. et al., 2025). These compounds exhibit potent antimicrobial properties and have been found to be effective against various bacterial and fungal infections. Furthermore, their antitubercular activity suggests potential applications in the treatment of tuberculosis (Sangaraiah Y.P. et al., 2022). Consequently, these compounds hold considerable promise for the pharmaceutical industry and the development of new and effective treatments for various diseases.

Various methods for synthesizing thiadiazole and oxadiazole derivatives have been extensively described in the literature. However, none of these methods is universally applicable, as each has certain limitations. These include the high cost of ionic liquids, the high toxicity of $POCl_3$, the limited applicability of polyphosphoric acid to certain substrates (Golovlyova S.M. et al., 2001), and the formation of by-products due to the high reactivity of methanesulfonic acid (Sharghi H. et al., 2005). Various approaches can be employed in syntheses using carboxylic acids. The structure and nature of the acid directly influence the choice of reaction conditions and the steps involved in the synthesis.

Specifically, 1,3,4-oxadiazoles and 1,3,4-thiadiazoles were synthesized in good yields through the cyclocondensation of adipic acid with semicarbazide and thiosemicarbazide, respectively, using $POCl_3$ as both a catalyst and a solvent.

Experimental Section

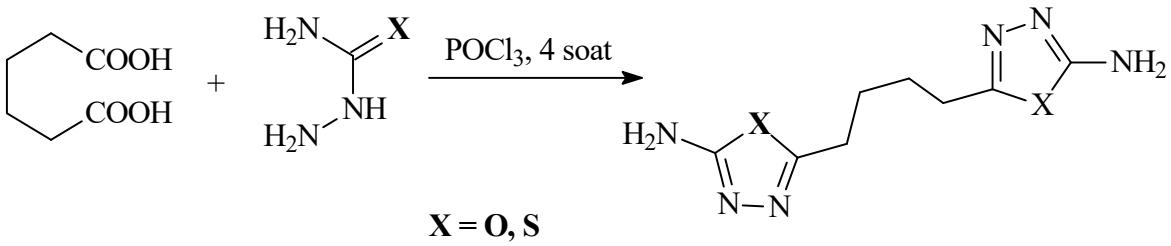
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A) Derivatives obtained from adipic acid and semicarbazide

A mixture of adipic acid (0.19 g) and semicarbazide (0.2 g) in a 1:2 molar ratio was stirred in the presence of $POCl_3$ and heated at 80–90 °C for 3 h. After the reaction, the mixture was cooled and poured into ice water, then neutralized with concentrated ammonia solution. The resulting precipitate was filtered off and recrystallized from water. Reaction progress was monitored by thin-layer chromatography (TLC) using chloroform–methanol as the solvent system (R_f = 0.68). The structure of the compound was established by IR and ^{1}H NMR spectroscopy.

B) Adipic acid (0.16 g) and thiosemicarbazide (0.2 g) were mixed in a 1:2 molar ratio. The reaction was carried out for 2 h. Reaction progress was monitored by thin-layer chromatography (TLC) using chloroform–methanol as the solvent system (R_f = 0.7). The melting point was 230–233 °C. The structure of the compound was established by IR and ^{1}H NMR spectroscopy.

The reaction can be represented by the following scheme.



X = O, S

In both reactions, the formation of adipic acid imide and monodiazoles was observed alongside the major bis-diazole products.

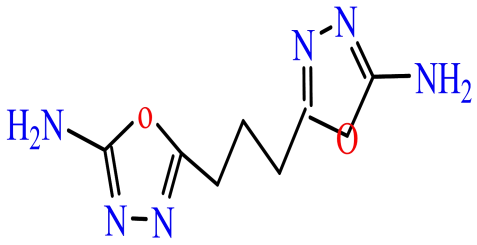
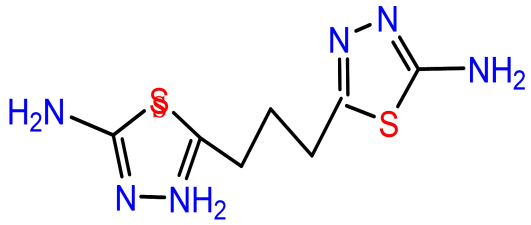
Table 1. Optimization of the reaction conditions for the synthesis of the compound.

№	Cyclizing reagent	Solvent	Temperature	Time	Yield (%)
1a	$POCl_3$	DMSO	80	2	88
2b	$POCl_3$	Chloroform	90	3	75

Table 2. Physical properties of the synthesized compounds.

№	Structure	Yield (%)	R_f	Melting point

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1.		88	EA\PE= (20:1) Rf=0.6	265°C
2.		61	EA\PE= (20:1) Rf=0.54	233°C

Parameters such as the numbers of hydrogen bond donor and acceptor groups fall within the optimal range. (Table 3)

2.2 The pharmacological and toxicity properties of compound 1b were evaluated using ADMET software.

In silico physicochemical and pharmacokinetic analysis. The physicochemical properties, lipophilicity, pharmacokinetics, and drug-likeness of the synthesized compound were evaluated using SwissADME. The compound has a molecular formula of $C_7H_{10}N_6S_2$ and a molecular weight of 242.32 g/mol, with 15 heavy atoms, including 10 aromatic heavy atoms. The fraction of sp^3-hybridized carbon atoms (Csp^3) was 0.43, with 4 rotatable bonds, 4 hydrogen bond acceptors, and 2 hydrogen bond donors. The molar refractivity was 61.25, and the topological polar surface area (TPSA) was 160.08 $Å^2$. According to SwissADME, TPSA is an important descriptor for assessing molecular polarity and certain ADME properties.

Lipophilicity analysis revealed that Log P_o/w values ranged from −0.36 to 2.42 across different prediction models. Specifically, the values were 1.30 for iLOGP, 0.76 for XLOGP3, 0.75 for WLOGP, −0.36 for MLOGP, and 2.42 for SILICOS-IT. The calculated consensus Log P_o/w was 0.97. In SwissADME, consensus Log P_o/w is defined as the mean of the values obtained from several independent prediction models.

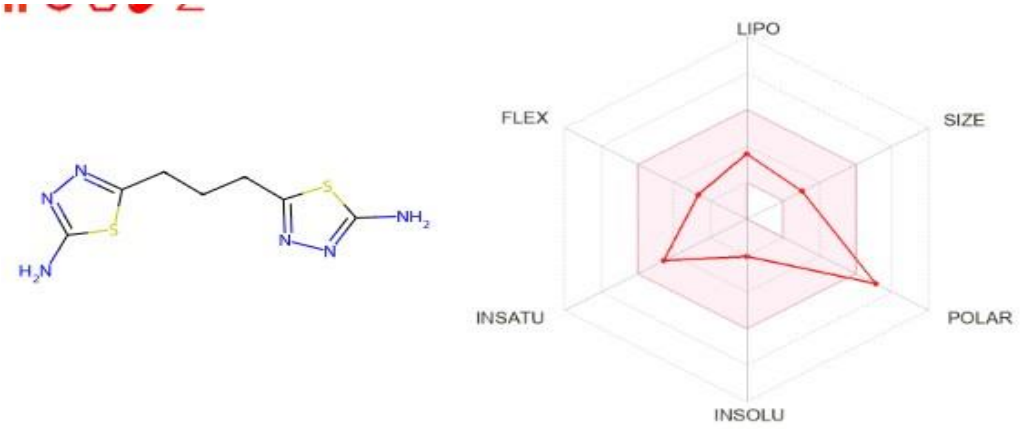
Regarding aqueous solubility, the ESOL model predicted a Log S of −2.05 and a solubility of 2.16 mg/mL (8.90×10^{-3} mol/L), classifying the compound as “soluble.” The Ali model predicted a Log S of −3.70 and a solubility of 4.82×10^{-2} mg/mL (1.99×10^{-4} mol/L), while the SILICOS-IT model predicted a Log S of −2.47 and a solubility of 8.27×10^{-1} mg/mL (3.41×10^{-3} mol/L). In SwissADME, Log S represents the base-10 logarithm of aqueous molar solubility.

Analysis of the pharmacokinetic parameters indicated low gastrointestinal absorption. The compound was predicted not to cross the blood–brain barrier (BBB) and to be a P-glycoprotein (P-gp) substrate. It was predicted to be non-inhibitory toward CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4. The predicted skin permeability was Log Kp = −7.24 cm/s. According to SwissADME, a more negative Log Kp value indicates lower skin permeability.

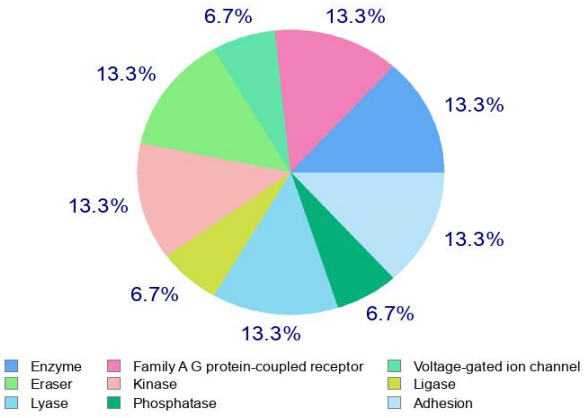
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Drug-likeness analysis showed that the compound satisfied Lipinski's rule of five with no violations and also passed the Ghose filter. However, it did not meet the Veber, Egan, and Muegge criteria, primarily because of its high TPSA. The bioavailability score was 0.55.
Medicinal chemistry analysis identified no alerts using either the PAINS or Brenk filters. Lead-likeness assessment revealed one violation associated with a molecular weight below 250 g/mol.

Analysis of the potential biological targets of the investigated compound suggested that it may interact with various protein classes. According to the diagram, the compound has a high predicted probability of binding to enzymes, G protein-coupled receptors (GPCRs), kinases, ion channels, erasers, and lyases (13.3% each). These findings suggest that it may influence metabolic processes, signal transduction, and intracellular regulation.



A lower probability (6.7%) was also observed for interactions with phosphatases, ligases, and adhesion-related proteins, suggesting that these targets play a secondary role.
Overall, the compound exhibits multi-target potential and may be considered a pharmacologically promising substance (Figure 1).



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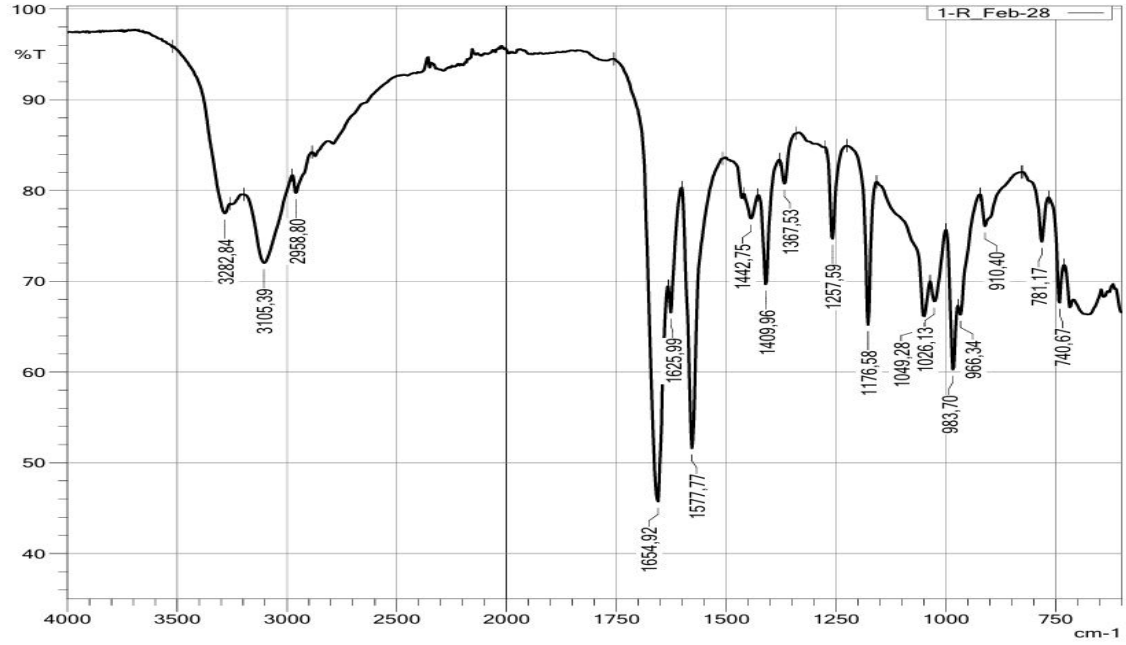
Figure 1

Percentage distribution of the major protein targets of compound 1a

5,5′-(Butane-1,4-diyl)bis(1,3,4-thiadiazol-2-amine). The oxadiazole compound shown to be bioactive also exhibits similar activity.

FTIR Analysis of 1,3,4-Thiadiazoles Synthesized from Adipic Acid and Thiosemicarbazide

IR spectral analysis. The absorption peak observed at 1654.92 cm^{-1} in the IR spectrum of the obtained compound corresponds to the C=N stretching vibration of the heterocyclic ring and represents one of the key diagnostic signals confirming the formation of the 1,3,4-thiadiazole ring. The signal at 1625.99 cm^{-1} may be attributed to vibrations associated with C=N/N–H groups in the conjugated ring system. The strong absorption band at 1026.13 cm^{-1} can reasonably be assigned to the N–N stretching vibration, consistent with the characteristic range for 1,3,4-thiadiazole systems.



The absorption bands in the 781.17–740.67 cm^{-1} range are associated with vibrations of the C–S bonds in the ring. The signal at 1577.77 cm^{-1} may be attributed to a complex vibrational mode involving C–N/C=N bonds within the ring. The signal at 983.70 cm^{-1} is assigned to an N–H bending vibration, specifically an out-of-plane mode; if present, N–H stretching vibrations are generally observed at higher wavenumbers, approximately 3200–3500 cm^{-1}.

Overall, the characteristic absorption bands at 1654.92, 1026.13, and 781.17–740.67 cm^{-1} support the presence of a 1,3,4-thiadiazole ring in the synthesized compound.

Conclusion. In this study, 2-amino-1,3,4-oxadiazole and thiadiazole derivatives were synthesized through the reaction of dicarboxylic acids with semicarbazide and thiosemicarbazide in the presence of $POCl_3$. The reaction mechanism was determined to involve the formation of a hydrazone as the acylation product of semicarbazide and thiosemicarbazide, followed by cyclodehydration to yield the target heterocyclic compound.

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The use of $POCl_3$ as both a solvent and a cyclizing agent in the synthesis of diazoles from the selected acid was found to improve product yield. Using the dehydrating agent in excess of the calculated stoichiometric amount helps provide mild and efficient reaction conditions. Thus, the selected method is characterized by its environmental safety, simplicity, and high efficiency and provides an important scientific basis for obtaining new biologically active compounds of pharmaceutical significance.

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