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Short Note

N-(4-Nitrophenyl)-2-{2-[3-(4-chlorophenyl)-5-[4-(propan-2-yl)phenyl]-4,5-dihydro-1*H*-pyrazol-1-yl]-4-oxo-4,5-dihydro-1,3-thiazol-5-yl}acetamide

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Abstract: In the present investigation, the synthesis and spectroscopic characterization of *N*-(4-nitrophenyl)-2-{2-[3-(4-chlorophenyl)-5-[4-(propan-2-yl)phenyl]-4,5-dihydro-1*H*-pyrazol-1-yl]-4-oxo-4,5-dihydro-1,3-thiazol-5-yl}acetamide (**2**) is performed. The title compound (**2**) is synthesized by the reaction of 3-(4-chlorophenyl)-5-[4-(propan-2-yl)phenyl]-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (**1**) with *N*-(4-nitrophenyl)maleimide. The cyclization of title compound is evidenced by FT-IR, NMR, and LCMS data.

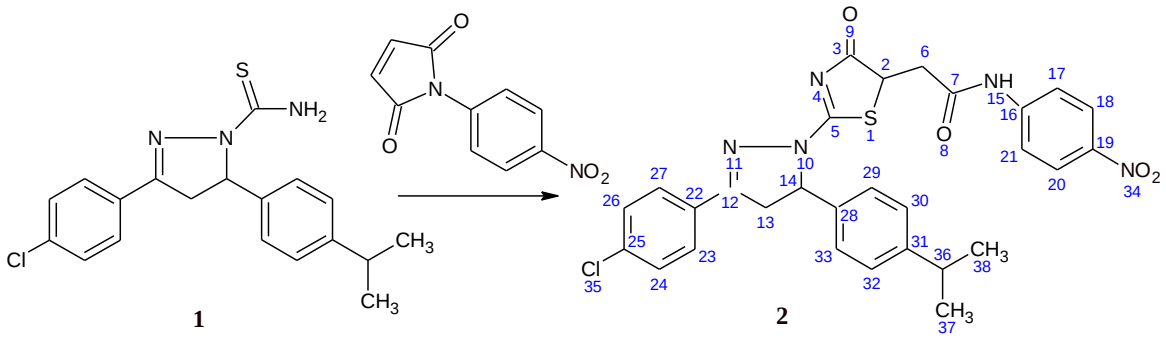
Keywords: thiazolidinone; pyrazoline; synthesis; maleimide

1. Introduction

The design, synthesis, and production of new heterocyclic molecules as therapeutic agents are the main objectives of organic and medicinal chemistry. A large number of drugs and biologically relevant molecules are heterocyclic in nature. Among the heterocyclic systems, there are numerous bioactive molecules comprised of five membered rings with two hetero atoms (i.e., nitrogen and sulfur). The thiazolidinone ring system is a core structure in various pharmaceutically important scaffolds and associated with various biological activities. Some prominent biological properties attributed to the thiazolidinone skeleton are antimicrobial [1], anticonvulsant [2], anti-HIV [3,4], anti-inflammatory [5], anticancer [6], antitubercular [7,8], antioxidant [9], antihistaminic [10], antiviral [11], and antidiabetic [12] activities. Motivated by the aforementioned findings and pursuing our studies on different heterocyclic compounds, we designed and synthesized a new substituted thiazolidinone derivative to test its potential biological utilities. The main objective of the present synthesis is to combine 4-thiazolidinone with substituted pyrazoline derivative.

2. Results

The synthetic pathway for title compound was carried out as outlined in Scheme 1. The substituted thiazolidinone derivative was obtained by the reaction of 3-(4-chlorophenyl)-5-[4-(propan-2-yl)phenyl]-4,5-dihydro-1*H*-pyrazole-1-carbothioamide with *N*-(4-nitrophenyl)maleimide under a reflux condition in glacial acetic acid [13,14]. The analytical and spectral data confirmed the structure and purity of the newly synthesized title compound (**2**).



Scheme 1. Synthesis of *N*-(4-nitrophenyl)-2-{2-[3-(4-chlorophenyl)-5-[4-(propan-2-yl)-phenyl]-4,5-dihydro-1*H*-pyrazol-1-yl]-4-oxo-4,5-dihydro-1,3-thiazol-5-yl}acetamide.

3. Discussion

The formation of the thiazolidinone scaffold from pyrazoline thiocarboamide was confirmed by the IR spectral data. The NH stretching frequency was observed at 3269 cm^{-1}. The stretching frequencies due to aromatic and aliphatic hydrogen appeared at 3088 cm^{-1} and 2962 cm^{-1}, respectively. The stretching frequencies at 1678 cm^{-1} and 1660 cm^{-1} corresponded to thiazolidinone and amide C=O, respectively. The characteristic absorption band appeared at 1597 cm^{-1} corresponding to the C=N group. The absorption bands for NO_2 asymmetric and symmetric stretching were seen at 1529 cm^{-1} and 1328 cm^{-1}, respectively. The C–Cl stretching frequency gave an absorption band at 833 cm^{-1}.

The ^{1}H-NMR spectrum displayed characteristic systems of two sets of AMX patterns due to pyrazoline moiety and 5-(2-oxoethyl)-4-thiazolidinone fragments. The chemical shifts for two diastereotopic methylene protons H_A and H_M at position 4 and a methine proton H_X at position 5 of the pyrazoline ring showed three doublet of doublets at δ 3.45 ppm (J_{AM} = 17.6 Hz, J_{AX} = 4.4 Hz), 4.05 ppm (J_{MA} = 18.4 Hz, J_{MX} = 11.2 Hz), and 5.77 ppm (J_{XA} = 3.6 Hz, J_{XM} = 11.2 Hz) and thiazolidinone oxoethyl moiety protons resonated at δ 2.73 ppm (J_{AM} = 16.8 Hz, J_{AX} = 4.0 Hz), 3.33 ppm (J_{MA} = 16.4 Hz, J_{MX} = 4.0 Hz), and 4.41 ppm (J_{XA} = 3.6 Hz, J_{XM} = 11.2 Hz), respectively. The singlet signal appeared at δ 10.75 ppm was assigned to the NH proton. The twelve aromatic protons appeared as a multiplet in the region 7.13–8.24 ppm. The methyl protons of isopropyl group appeared as a doublet at δ 1.16 ppm with J = 7.2 Hz, whereas the methine proton resonated as a multiplet in the region δ 2.84–2.89 ppm.

In the ^{13}C-NMR spectrum, the signals at δ 187.8 ppm and 176.9 ppm corresponded to C-3 and C-7 carbonyl (C=O) carbons of thiazolidinone and amide group, respectively. The C-5 and C-12 carbons resonated signals at δ 169.6 and 159.7 ppm respectively which corresponded to C=N of thiazolidinone and pyrazoline moieties. The C-19 carbon displayed a signal at δ 148.0 ppm was due to *ipso* carbon attached to the *p*-nitrophenyl moiety. The C-2 carbon of the thiazolidinone ring displayed a signal at δ 49.9 ppm. The signals at δ 63.5 and 43.2 ppm attributed to the C-14 and C-13 carbons of the pyrazoline ring. The C-6 methylene carbon resonated a signal at δ 35.7 ppm. The signals for C-36 and C-37/C-38 carbons of isopropyl group resonated at δ 33.0 and 23.7 ppm, respectively. LCMS spectrum supported the purity and molecular weight of the compound and displayed a molecular ion peak *m/z* at 577.7 (M^+ + 1), which corresponded to the molecular formula, $C_{29}H_{26}ClN_5O_4S$. As the title compound possesses two chiral centers, so the possibility of four optical isomers could be envisaged. However, no attempt has been made to separate the isomers.

4. Materials and Methods

All the reagents and solvents were purchased from Sigma-Aldrich India and used without further purification. The melting point was taken in an open capillary tube and was uncorrected. The purity of the compound was confirmed by thin layer chromatography using Merck (Darmstadt, Germany) silica gel 60 F_{254}-coated aluminum plates. IR spectrum was recorded on Shimadzu-FTIR Infrared spectrometer (Shimadzu, Kyoto, Japan) (ν_{max} in cm^{-1}). ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz)

spectra recorded on a Bruker Avance III (Bruker, Billerica, Massachusetts, MA, USA), 400 MHz in DMSO-d_6 solvent with 5 mm PABBO BB-1H tubes and TMS as internal standard. LCMS was obtained using Agilent (Santa Clara, California, CA, USA) 1200 series LC and Micromass zQ spectrometer. Elemental analysis was carried out by using VARIO EL-III (Elementar Analysensysteme GmBH, Hanau, Germany).

The synthesis and crystal structure of the starting material, 3-(4-chlorophenyl)-5-[4-(propan-2-yl) phenyl]-4,5-dihydro-1*H*-pyrazole-1- carbothioamide (**1**) was described in our earlier work [15–17].

A mixture of 3-(4-chlorophenyl)-5-[4-(propan-2-yl)phenyl]-4,5-dihydro-1*H*-pyrazole-1- carbothioamide (10 mmol) and *N*-(4-nitrophenyl)maleimide (10 mmol) was refluxed for 5 h in glacial acetic acid (15 mL). Completion of the reaction was checked by thin layer chromatography and the reaction mixture was cooled to room temperature and poured onto ice cold water. The precipitate obtained was filtered off, washed with water, dried, and recrystallized in DMF. Yield was 74 %.

Melting point: 266–268 °C; LCMS: m/z = 577.7 (M^+ + 1); FTIR: ν_{max} (cm^{-1}), 3269 (NH), 3088 (Ar-H), 2962 (Al-H), 1678 (thiazolidinone C=O), 1660 (amide C=O), 1597 (C=N), 1529 (C-NO_2 asymmetric stretching), 1328 (C-NO_2 symmetric stretching), 833 (C–Cl); ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm, 1.16 (d, 6H, CH_3, J = 7.2 Hz), 2.84–2.89 (m, 1H, CH), 2.73 (dd, 1H, thiaz H_A, J_{AM} = 16.8 Hz, J_{AX} = 4.0 Hz), 3.33 (dd, 1H, thiaz H_M, J_{MA} = 16.4 Hz, J_{MX} = 4.0 Hz), 3.45 (dd, 1H, pyraz H_A, J_{AM} = 17.6 Hz, J_{AX} = 4.4 Hz), 4.05 (dd, 1H, pyraz H_M, J_{MA} = 18.4 Hz, J_{MX} = 11.2 Hz), 4.41 (dd, 1H, thiaz CH, J_{XA} = 4.0 Hz, J_{XM} = 11.2 Hz), 5.77 (dd, 1H, pyraz H_X, J_{XA} = 3.6 Hz, J_{XM} = 11.2 Hz), 7.13–8.24 (m, 12H, Ar-H), 10.75 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ ppm, 23.7 (C-37/C-38, CH_3), 33.0 (C-36, CH), 35.7 (C-6, CH_2), 43.2 (C-13, pyrazoline CH_2), 49.9 (C-2, CH of thiazolidinone ring), 63.5 (C-14, pyrazoline CH), 118.8, 124.9, 125.5, 125.6, 126.8, 128.5, 129.0, 136.1, 136.2, 137.6, 137.7, 142.2, 144.8, 147.9, 148.0 (aromatic C′s), 159.7 (C-12, C=N of pyrazoline ring), 169.6 (C-5, C=N of thiazolidinone ring), 176.9 (C-7, amide C=O), 187.8 (C-3, thiazolidinone C=O); Elemental analysis: Calculated for $C_{29}H_{26}ClN_5O_4S$, C, 60.46 %; H, 4.55 %; N, 12.16 %. Found: C, 60.44 %; H, 4.58 %; N, 12.14 %.

5. Conclusions

In the present study, a simple and effective method of synthesizing a new heterocycle 5-substituted thiazolidinone integrated with a pyrazoline derivative was reported. The structure of the title compound was confirmed by analytical and spectroscopic data.

Supplementary Materials: The FTIR, ^{1}H-NMR, ^{13}C-NMR, and LCMS data are available online.

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Author Contributions: V.V.S. performed the experiments; B.K.S. analyzed the data; B.N. guided throughout the research work.

Conflicts of Interest: The authors declare no conflict of interest.

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