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Synthesis and DFT study of novel pyrazole, thiophene, 1,3-thiazole and 1,3,4-thiadiazole derivatives

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ABSTRACT

Regioselective facile synthesis of innovative heterocycles from the reaction of 2-cyano-*N*-cyclohexylacetamide (3) with hydrazonoyl chloride (4) in basic condition afforded amino pyrazole derivative 6. The behavior of acetamide 3 with phenylisothiocyanate in DMF/KOH surveyed by addition of the α-halo ketones to yeild the corresponding thiophene derivative 13a, 13b, 16, 18 and 1,3-thiazoles 21. Reaction of intermediate potassium salt 9 with hydrazonoyl chloride 22a-e furnished the corresponding 1,2,4-thiadiazoles 24a-e. Density functional theory (DFT) calculations at the B3LYP and HF techniques combined with 6-31G(d) basis set to investigate the equilibrium geometry of the innovative compound pyrazoles 6 and the stability affording of HOMO/LUMO molecular orbitals.

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1. Introduction

Cyanoacetamide derivatives are polyfunctional and extremely sensitive, which grip both electrophilic and nucleophilic interiors. Two of the nucleophilic interiors in cyanoacetamides are limited on the NH and the C-2 positions with a reactivity instruction, C-2 > NH. Two electrophilic positions are attached with the C-1 and C-3 situations with reactivity order C-3 > C-1 (Figure 1) [1-5]. Cyanoacetamide active synthons are successfully used for the creations of numerous open-chain groups and poly substituted heterocyclic moieties [6-8]. The occurrence of two electron-withdrawing groups' outcomes in the extraordinary action of cyanoacetamides as CH acidic and the active methylene worth they can be included in a variability of condensation and substitution reactions [9-11].

Additionally, their carbonyl and the cyano functional groups help them to re-join with common reagents to form a diversity of heterocyclic compounds for instance, type-in thiophene [12], pyrazole [13], thiazole [14-16], 1,3-dithiazole, 1,3-dithiane [17], pyridine[18-21], chromene and coumarin derivatives [22,23]. Additionally, cyanoacetamide derivatives were exploited as animated precursors for the production of polycondensed N/O/S heterocyclic compounds [22-24].

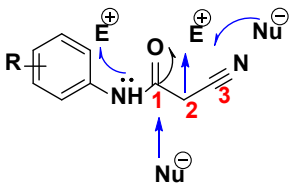

Figure 1. Cyanoacetamide derivatives reactivity.

Upon a comprehensive investigation of the procedures for the preparation and chemical reactivity of cyanoacetamide derivatives, we institute that synthesis of cyanoacetamides

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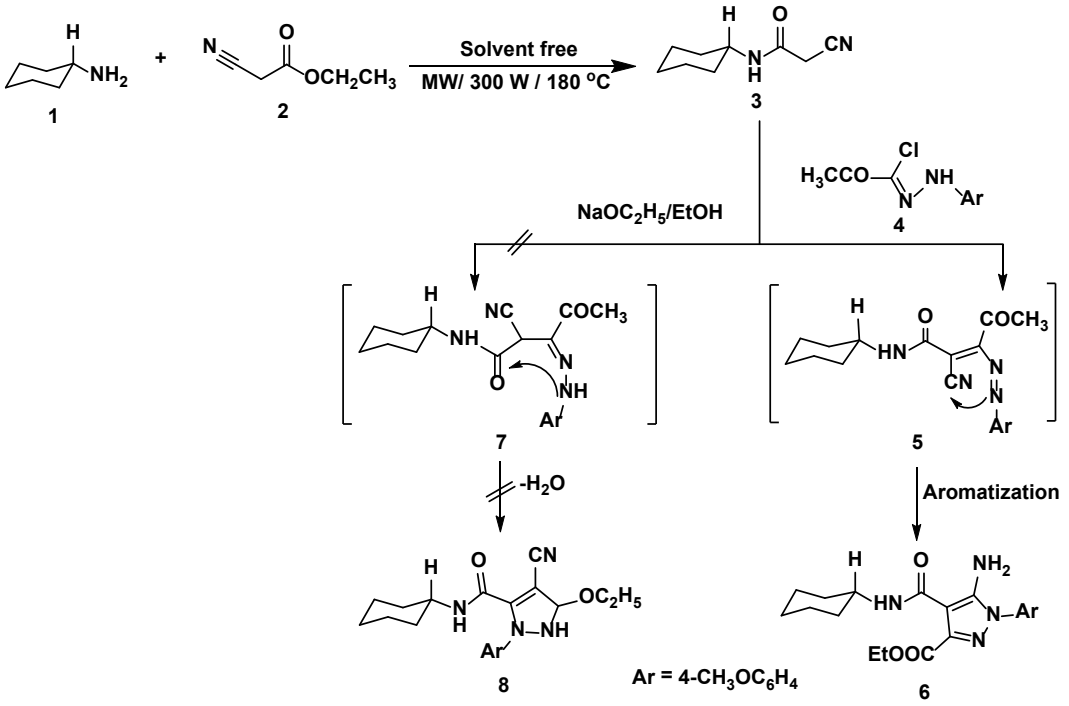


Scheme 1

may possibly exist applicable a numerous techniques. The greatest versatile and routinely used preparative method is the acylation of aromatic or heterocyclic amines with ethyl cyanoacetate further down numerous reaction conditions [25]. Our improvement research, to institute that the hitherto unreported 2-cyano-*N*-cyclohexylacetamide (**3**) is a extremely versatile structure block for the production of an extensive variety of numerous innovative fused heterocyclic moieties. We proficient theoretical studies on the furthermost encouraging fused heterocyclic compounds by exhausting the HF/6-31G (d) and DFT (B3LYP/6-31G(d)) techniques [26,27] highly resourceful building block for the synthesis of an extensive diversity of numerous innovative pyridine-based heterocyclic derivatives. We consummate theoretical studies on the furthermost encouraging fused heterocyclic compounds through exhausting the HF and DFT processes [28,29] utilizing Gaussian 09W [30].

2. Experimental

2.1. General

Gallenkamp melting point apparatus was used for measuring the melting points. Moreover, Shimadzu FT-IR 8101 PC infrared spectrophotometer recorded the IR spectra. The ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$ or DMSO-d_6 at 300 MHz on a Varian Mercury VX 300 NMR spectrometer (^{1}H at 300 MHz, ^{13}C at 75 MHz) exhausting trimethyl silane as an internal typical. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Elemental analyses were approved out at the Micro-analytical Center of Cairo University, Giza, Egypt. Microwave experiments were carried out using CEM Discover™ microwave apparatus.

2.2. Material and reagents

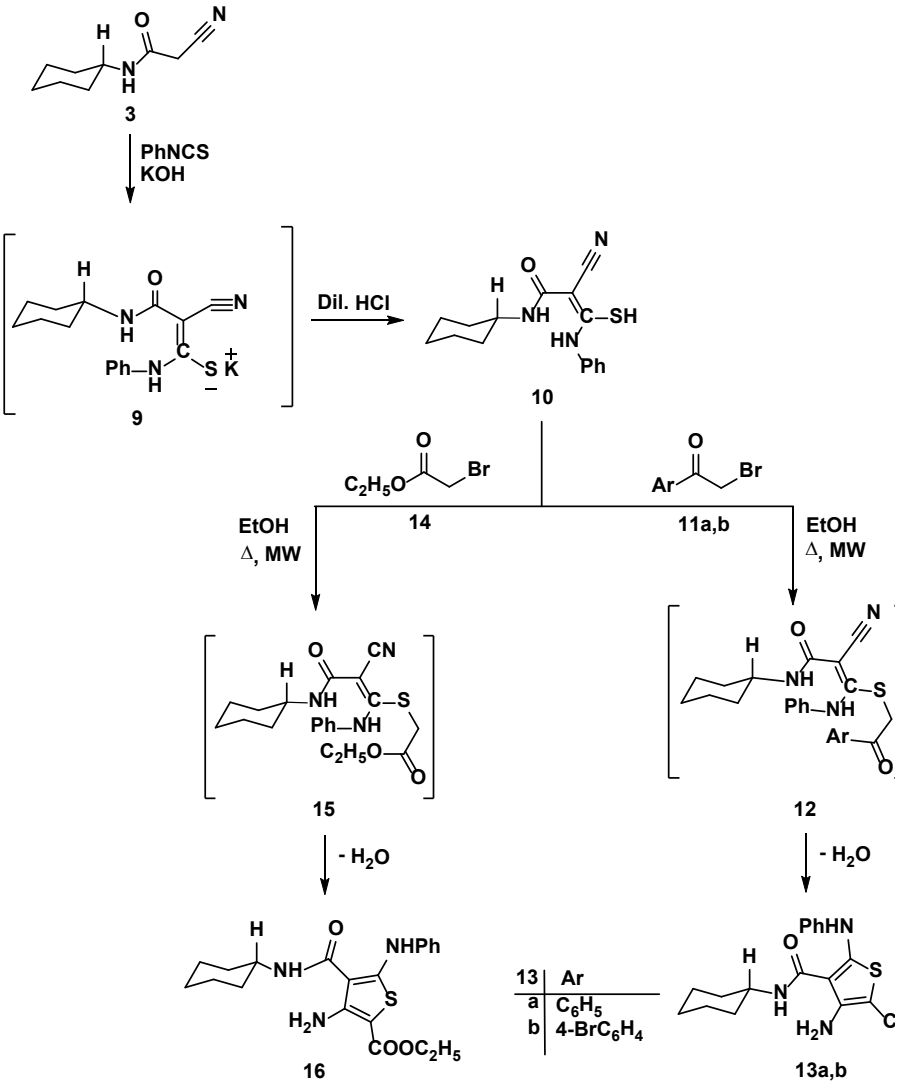
Cyclohexylamine, ethylcyanoacetate, phenyl isothiocyanate, dimethylformamide, potassium hydroxide, bromo-1-phenylethanone, ethyl bromoacetate, chloroacetonitrile, chloroacetone, ethanol and triethylamine were purchased from Aldrich Chemical Co. Methanol, petroleum ether, chloroform were purchased from BDH reagents. Hydrazonoyl chlorides (**4**), benzylidenecyanoacetate (**22a-e**) were synthesised following literature processes [20,21].

2.3. Synthesis 2-cyano-N-cyclohexylacetamide (3)

Cyclohexylamine mixture (**1**) (1.5 g, 10 mmol) and ethyl cyanoacetate (**2**) (1.1 g, 10 mmol) was mixed in a process vial. The vial capped properly and irradiated with microwave underneath pressurized environments (17.2 bar, 180 °C) on behalf of 5 min. The reaction mixture was disappeared in vacuo and residual solid was occupied in ether, formerly together through filtration wash away, dried and finally crystallized from ethanol:DMF (2:1, *v*:*v*) to give white crystal of 2-cyano-*N*-cyclohexylacetamide (**3**) (Scheme 1) [31,32]. Color: White. Yield: 90%. M.p.: 126-128 °C. FT-IR (KBr, ν, cm^{-1}): 1662 (C=O), 2204 (CN), 3278 (NH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.40-1.70 (m, 10H, HC-aliphatic), 3.30 (s, 2H, H_2C), 3.55 (s, 1H, HC), 8.08 (s, 1H, HN, D_2O-exchangable). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 24.3 (CH_2), 25.3 (CH_2), 27.3 (CH_2), 34.3 (CH_2), 47.1 (CH), 125.7(CN), 171.2 (C=O). MS (*m*/*z* (%)): 166 (M^+, 100.0), 123 (75.3), 56 (7.3), 82 (86.9). Anal. calcd. for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 65.08; H, 8.51; N, 16.89%.

2.4. Reactions of 2-cyano-N-cyclohexylacetamide (3) with hydrazonoyl halides (4)

General procedure: 2-Cyano-*N*-cyclohexylacetamide (**3**) (0.166 g, 1 mmol) was added to an ethanolic sodium ethoxide solution [prepared from sodium metal (0.02 g, 1 mmol) and absolute ethanol (15 mL)] with stirring. After stirring for 20 minutes, the appropriate hydrazonoyl halides (**4**) (1 mmol) was added portion wise to the resulting solution and the reaction mixture was stirred for further 12 h at room temperature.



Scheme 2

The solid that formed was filtered off, washed with water and dried. Recrystallization from the proper solvent afforded the aminopyrazole derivatives (**6**) (Scheme 1).

Ethyl 5-amino-4-(cyclohexylcarbamoyl)-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylate (**6**): Color: Pale yellow. Yield: 70%. M.p.: >300 °C. FT-IR (KBr, ν, cm^{-1}): 1691 (C=O), 3280 (NH_2), 3409 (NH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.39-1.49 (m, 10H, H_2C), 1.52 (t, 3H, H_3C), 3.54 (s, 1H, *H*C-NH), 3.73 (s, 3H, H_3C), 4.29 (q, 2H, H_2C), 6.52 (s, 2H, H_2N D_2O-exchangable), 6.80 (s, 2H, HC), 7.20 (s, 2H, HC), 8.05 (s, 1H, HN D_2O-exchangable). ^{13}C NMR (75 MHz, DMSO, δ, ppm): 15.3 (CH_3), 25.3 (CH_2), 28.2 (CH_2), 34.3 (CH_2), 47.1 (CH), 54.3 (OCH_3), 62.8 (CH_2), 96.2 (CH), 115.7 (CH), 124.1 (CH), 133.2 (CH), 142.3 (CH=), 148.3 (CH), 162 (C=O), 167 (C=O). MS (EI, *m/z* (%)): 386 (M^+, 100.0), 370 (21.0), 315 (45.4). Anal. calcd. for $C_{20}H_{26}N_4O_4$: C, 62.16; H, 6.78; N, 14.50. Found: C, 62.22; H, 6.82; N, 14.53%.

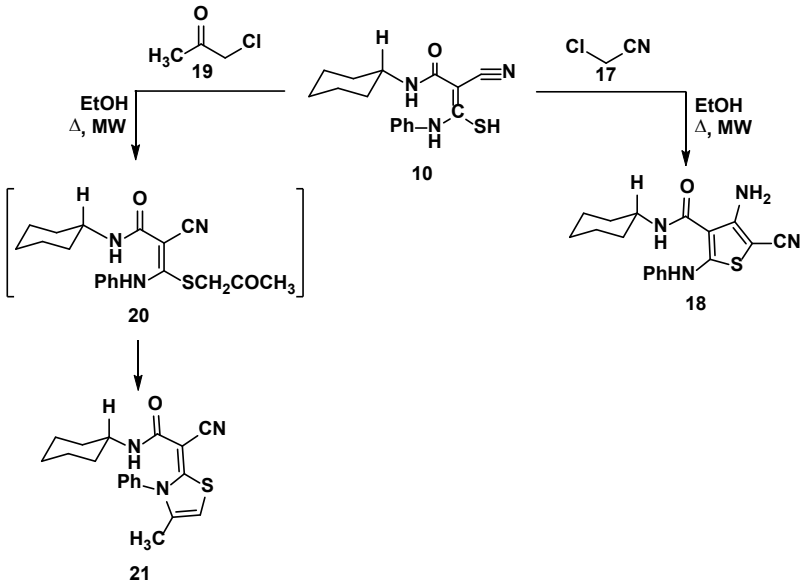
2.5. Reaction of 2-cyano-N-cyclohexylacetamide (3) with phenyl isothiocyanate

General procedure: Potassium hydroxide solution (0.11 g, 2 mmol) in dimethyl formamide (20 mL) was auxiliary to 2-cyano-*N*-cyclohexylacetamide (**3**) (0.332 g, 2 mmol). Afterward stirring for 30 min, phenyl-isothiocyanate (0.24 mL, 2 mmol) was further to the subsequent mixture and stirring was sustained for 6 h, formerly decant over crushed ice containing hydrochloric acid. The formed product was filtered off, washed with water, dried and finally recrystallized from the proper solvent (Scheme 2).

2-Cyano-N-cyclohexyl-3-mercapto-3-(phenylamino)acrylamide (**10**): Color: Yellow. Yield: 80%. M.p.: 152-154 °C. FT-IR (KBr, ν, cm^{-1}): 1670 (C=O), 2250 (C=N), 3266 (NH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.37-1.52 (m, 10H, H_2C), 3.55 (s, 1H, *H*C-NH), 7.33-7.74 (m, 5H, Ar-H), 7.91 (s, 1H, HC), 10.88 (s, 1H, HN D_2O-exchangable), 11.83 (s, 1H, HS D_2O-exchangable). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 23.2 (CH_2), 27.3 (CH_2), 32.3 (CH_2), 43.5 (CH), 88.0 (CH), 115.0 (CH), 118.3 (CH), 142.0 (CH), 96.2 (CH), 115.7 (CN), 124.1 (CH), 133.2 (CH), 142.3 (CH=), 148.3 (CH), 159.0 (C=O). MS (*m/z* (%)): 301 (M^+, 100.0), 268 (65.3). Anal. calcd. for $C_{16}H_{19}N_3OS$: C, 63.67; H, 6.35; N, 13.94. Found: C, 63.70; H, 6.40; N, 13.90%.

2.6. Reaction of 2-cyano-N-cyclohexyl-3-mercapto-3-(phenyl amino)acrylamide (10) with α-haloketones

Thermal method: Mixture of 2-cyano-*N*-cyclohexyl-3-mercapto-3-(phenylamino) acrylamide (**10**) (0.3 g, 1 mmol)



Scheme 3

treated with *α*-haloketones (1 mmol) with absolute alcohol (20 mL) with few drops of triethylamine as a catalyst formed solid after reflux for 2h. The solid product so formed was filtered off, washed with water, dried and finally recrystallized from the proper solvent to afford compounds **13a**, **13b**, **16**, **18** and **21** (Scheme 2 and 3).

Microwave method: Ethanolic mixture of 2-cyano-*N*-cyclo hexyl-3-mercapto-3-(phenylamino) acrylamide (**10**) (0.3 g, 1 mmol) reacts with α-haloketones (1 mmol) with few drops of triethylamine was mixed in a process vial. The vial capped properly and irradiated by microwaves using pressurized conditions (17.2 bar, 150 °C) for 3 min, the reaction mixture was evaporated in vacuo and residual solid was taken in ethanol then collected by filteration, washed, dried and finally recrystalized from the proper solvent to afford compounds **13a**, **13b**, **16**, **18** and **21**.

4-Amino-5-benzoyl-N-cyclohexyl-2-(phenylamino)thiophe ne-3-carboxamide (**13a**): Color: Reddish brown. Yield: 80%. M.p.: 256-258 °C. FT-IR (KBr, ν, cm^{-1}): 1620 (C=O), 3297 (NH_2), 3556 (NH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.40-1.70 (m, 10H, H_2C), 3.55 (s, 1H, *H*C-NH), 6.22 (s, 2H, H_2N D_2O-exchangable), 6.46-7.01 (m, 5H, Ar-H), 7.45 (m, 3H, HC), 7.81 (d, *J* = 2.1 Hz, 2H, HC), 8.05 (s, 1H, HN D_2O-exchangable), 9.51 (s, 1H, HN D_2O-exchangable). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 24.6 (CH_2), 28.1 (CH_2), 34.5 (CH_2), 92.3 (CH), 103.2 (CH), 116.0 (CH), 128.3 (CH), 129.3 (CH), 133.3 (CH), 136.0 (CH), 143.2 (CH), 167.3 (C=O), 180.0 (C=O). MS (*m/z* (%)): 419 (M$^+$, 100), 126 (12.3), 321 (33.2). Anal. calcd. for $C_{24}H_{25}N_3O_2S$: C, 68.71; H, 6.01; N, 10.02. Found: C, 68.75; H, 6.07; N, 10.07%.

4-Amino-5-(4-bromobenzoyl)-N-cyclohexyl-2-(phenylamino) thiophene-3-carboxamide (**13b**): Color: Brown. Yield: 80%. M.p.: 260-262 °C. FT-IR (KBr, ν, cm^{-1}): 1620 (C=O), 3285 (NH_2), 3356 (NH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.37-1.52 (m, 10H, H_2C), 3.42 (s, 1H, HC-NH), 6.22 (s, 2H, H_2N D_2O-exchangable) 7.05-7.38 (m, 5H, Ar-H), 7.52 (d, *J* = 3.2 Hz, 2H, HC), 7.68 (d, *J* = 7.6 Hz, 2H, HC), 7.912 (s, 1H, HN D_2O-exchangable), 9.76 (s, 1H, HN D_2O-exchangable). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 23.4 (CH_2), 25.3 (CH_2), 32.5 (CH_2), 94.3 (CH), 105.7 (CH), 114.2 (CH), 118.6 (CH), 127.3 (CH), 129.3 (CH), 132.3 (CH), 134.3 (CH), 143.2 (CH), 167.3 (C=O), 169.2 (CH=), 182.2 (C=O). MS (*m/z* (%)): 498 (M$^+$, 100.0), 497 (35.2), 331 (41.00). Anal. calcd. for $C_{24}H_{24}BrN_3O_2S$: C, 57.83; H, 4.85; N, 8.43. Found: C, 57.85; H, 4.88; N, 8.47%.

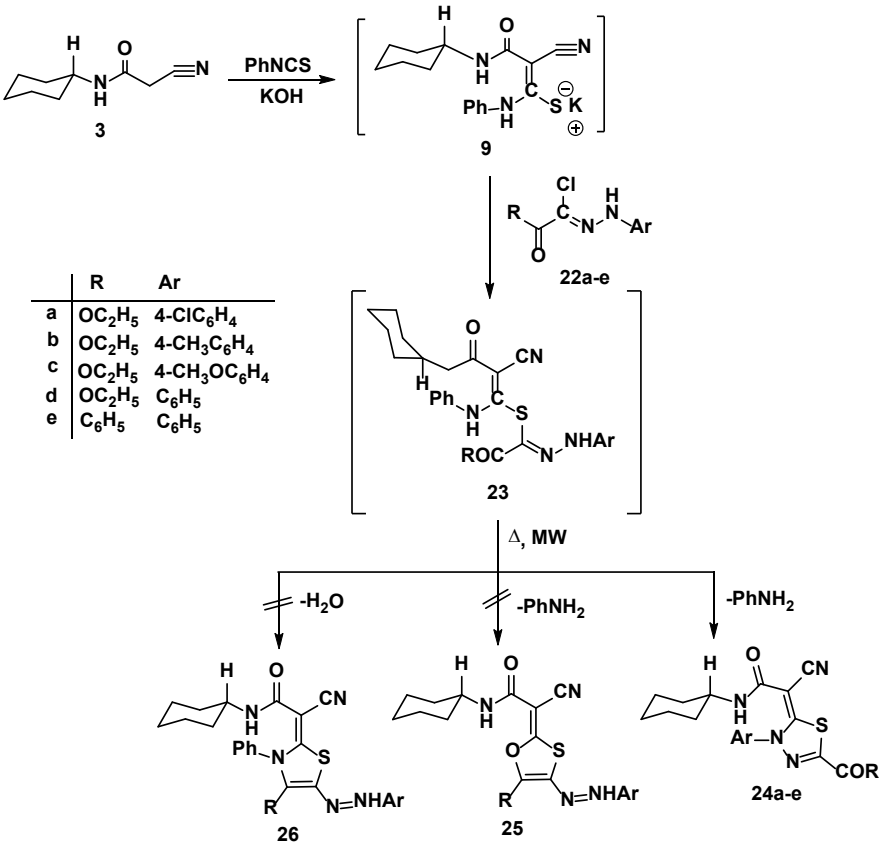
Ethyl 3-amino-4-(cyclohexylcarbamoyl)-5-(phenylamino) thiophene-2-carboxylate (**16**): Color: Dark yellow. Yield: 80%. M.p.: 160-162 °C. FT-IR (KBr, ν, cm^{-1}): 1654 (C=O), 3332 (NH_2), 3428 (NH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.43-1.65 (m, 10H, H_2C), 1.79 (t, 3H, H_3C), 3.53 (s, 1H, HC-NH), 4.183 (q, 2H, H_2C), 6.61 (s, 2H, H_2N D_2O-exchangable), 7.02-7.21 (m, 5H, Ar-H), 7.932 (s, 1H, HN D_2O-exchangable), 9.66 (s, 1H, HN, D_2O-exchangable). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 14.3 (CH_3), 24.3 (CH_2), 28.3 (CH_2), 48.3 (CH), 60.3 (CH_2), 103.7 (CH) 116.2 (CH), 118.6 (CH), 120.5 (CH), 129.3 (CH), 133.3 (CH), 143.2 (CH), 160 (C=S), 167.2 (CH=), 169.2 (C=O). MS (*m/z* (%)): 387 (M$^+$, 100.0), 341 (18.3), 288 (7.5). Anal. calcd. for $C_{20}H_{25}N_3O_3S$: C, 61.99; H, 6.50; N, 10.84. Found: C, 61.92; H,6.46; N, 10.80%.

4-Amino-5-cyano-N-cyclohexyl-2-(phenylamino) thiophene-3-carboxamide (**18**): Color: Yellow. Yield: 75%. M.p.: 158-160 °C. FT-IR (KBr, ν, cm^{-1}): 1650 (C=O), 2250 (C=N), 3250 (NH_2), 3428 (NH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.35-1.55 (m, 10H, H_2C), 3.481 (s, 1H, *H*C-NH), 6.60 (s, 2H, H_2N D_2O-exchangable), 7.02-7.21 (m, 5H, Ar-H), 7.862 (s, 1H, HN D_2O-exchangable), 9.60 (s, 1H, HN D_2O-exchangable). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 24.6 (CH_2), 28.3 (CH_2), 47.6 (CH), 85.3 (CH), 115.3 (CN), 116.2 (CH), 118.6 (CH), 129.3 (CH), 133.3 (CH), 138.2 (CH), 168.4 (C=O). MS (*m/z* (%)): 340 (M$^+$, 100.0), 257 (14.3), 123.2 (15.3). Anal. calcd. for $C_{18}H_{20}N_4OS$: C, 63.50; H, 5.92; N, 16.46. Found: C, 63.54; H, 5.96; N, 16.48%.

2-Cyano-N-cyclohexyl-2-(4-methyl-3-phenylthiazol-2(3H)-ylidene)acetamide (**21**): Color: Brown. Yield: 85%. M.p.: 210-212 °C. FT-IR (KBr, ν, cm^{-1}): 1616 (C=O), 2163 (C=N), 3419 (NH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.03-1.09 (m, 10H, H_2C), 2.08 (s, 3H, H_3C), 3.57 (s, 1H, HC-NH), 6.77 (s, 1H, HC=), 7.41-7.51 (m, 5H, Ar-H), 7.801 (s, 1H, HN D_2O-exchangable). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 16.3 (CH_3), 24.3 (CH_2), 28.6 (CH_2), 47.6 (CH), 78.3 (CH), 110.0 (CH=), 142.3 (CH=), 160.3 (C=O), 168.4 (CH=). MS (*m/z* (%)): 339 (M$^+$, 100), 284 (14.6). Anal. calcd. for $C_{19}H_{21}N_3OS$: C, 67.23; H, 6.24; N, 12.38. Found: C, 67.19; H, 6.26; N, 12.39%.

2.7. Reaction of 2-cyano-N-cyclohexyl-3-mercapto-3-(phenyl amino)acrylamide (9) with hydrozonyl derivatives

Thermal method: Ethanolic solution of acrylamide (**9**) (0.3 g, 1 mmol) treated with hydrazonyl chloride derivatives (**22a**-



Scheme 4

e) (1 mmol) with little amount of triethylamine as a catalyst formed green solid afterward reflux for 6 h. The solid product formed and filtered off, washed with water, dried and finally recrystallized from the proper solvent to afford compounds **24a**-**e** (Scheme 4).

Microwave method: Acrylamide solution (**9**) (0.3 g, 1 mmol) reacts with hydrazonyl derivatives **22a**-**e** (1 mmol) with few drops of triethylamine was mixed in a process vial. The vial capped properly and irradiated by microwaves using pressurized conditions (17.2 bar, 150 °C) for 20 min, the reaction mixture was evaporated in vacuo and residual solid was taken in ethanol then collected by filteration, washed, dried and finally recrystalized from the proper solvent to afford the corresponding compounds **24a**-**e**.

Ethyl-4-(4-chlorophenyl)-5-(1-cyano-2-(cyclohexylamino)-2-oxoethylidene)-4, 5-dihydro-1, 3, 4-thiadiazole-2-carboxylate (**24a**): Color: Yellow powder. Yield: 75%. M.p.: 218-220 °C. FT-IR (KBr, ν, cm^{-1}): 1620 (C=O), 2191 (C=N), 3340 (NH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.32-1.42 (m, 10H, H_2C), 1.823 (t, 3H, H_3C), 3.531 (s, 1H, *H*C-NH), 4.20 (q, 2H, H_2C), 6.40-7.21 (m, 4H, Ar-H), 7.86 (s, 1H, HN D_2O-exchangable). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 12.3 (CH_3), 22.3 (CH_2), 28.6 (CH_2), 47.6 (CH), 60.3 (CH_2), 87.3 (CH=), 115.3 (CN), 117.3 (CH), 124.3 (CH), 129.3 (CH), 144.3 (CH), 154.0 (CH=S), 158.3 (C=O), 162.3 (C=O). MS (*m/z* (%)): 432 (M^+, 100.0), 434 (36.8). Anal. calcd. for $C_{20}H_{21}ClN_4O_3S$: C, 55.49; H, 4.89; N, 12.94. Found: C, 55.52; H, 4.85; N, 12.90%.

Ethyl-5-(1-cyano-2-(cyclohexylamino)-2-oxoethylidene)-4-(p-tolyl)-4, 5-dihydro-1,3,4-thiadiazole-2-carboxylate (**24b**): Color: Pale yellow. Yield: 70%. M.p.: 168-170 °C. FT-IR (KBr, ν, cm^{-1}): 1619 (C=O), 2190 (C=N), 3342 (NH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.33-1.47 (m, 10H, H_2C), 1.69 (t, 3H, H_3C), 2.35 (s, 3H, H_3C), 3.66 (s, 1H, *H*C-NH), 4.20 (q, 2H, H_2C), 6.34 (d, 2H, J = 1.2 Hz, Ar-H), 6.81 (d, 2H, *J* = 1.2 Hz, Ar-H), 7.89 (s, 1H, HN D_2O-exchangable). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 13.6 (CH_3), 22.3 (CH_3), 23.3 (CH_2), 28.6 (CH_2), 47.6 (CH), 60.3 (CH_2), 88.4 (CH=), 115.3 (CN), 128.3 (CH), 129.3 (CH), 143.6 (CH), 154.0 (CH=S), 159.5 (C=O), 161.6 (C=O). MS (*m/z* (%)): 412 (M^+, 100.0), 384 (75). Anal. calcd. for $C_{21}H_{24}N_4O_3S$: C, 61.15; H, 5.86; N, 13.58. Found: C, 61.17; H, 5.89; N, 13.63%.

Ethyl-5-(1-cyano-2-(cyclohexylamino)-2-oxoethylidene)-4-(4-methoxyphenyl)-4,5-dihydro-1, 3, 4-thiadiazole-2-carboxylate (**24c**): Color: Yellow. Yield: 70%. M.p.: 170-172 °C. FT-IR (KBr, ν, cm^{-1}): 1623 (C=O), 2186 (C=N), 3345 (NH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.29-1.42 (m, 10H, H_2C), 1.78 (t, 3H, H_3C), 3.523 (s, 1H, *H*C-NH), 3.64 (s, 3H, H_3C), 4.20 (q, 2H, H_2C), 6.34-6.63 (m, 4H, Ar-H), 7.832 (s, 1H, HN D_2O-exchangable). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 13.8 (CH_3), 23.3 (CH_3), 28.6 (CH_2), 47.6 (CH), 60.7 (CH_2), 113.2 (CH), 115.3 (CN), 119.3 (CH), 129.3 (CH), 139.3 (CH), 154.0 (CH=S), 160.2 (C=O). MS (*m/z* (%)): 428 (M^+, 100.0). Anal. calcd. for $C_{21}H_{24}N_4O_4S$: C, 58.86; H, 5.65; N, 13.07. Found: C, 58.91; H, 5.62; N, 13.11%.

Ethyl-5-(1-cyano-2-(cyclohexylamino)-2-oxoethylidene)-4-phenyl-4, 5-dihydro-1, 3, 4-thiadiazole-2-carboxylate (**24d**): Color: Pale yellow. Yield: 75%. M.p.: 204-206 °C. FT-IR (KBr, ν, cm^{-1}): 1681 (C=O), 2169 (C=N), 3243 (NH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.30-1.40 (m, 10H, H_2C), 1.79 (t, 3H, H_3C), 3.72 (s, 1H, HC-NH), 4.20 (q, 2H, H_2C), 6.50-7.06 (m, 5H, Ar-H), 8.001 (s, 1H, HN D_2O-exchangable). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 13.8 (CH_3), 23.3 (CH_3), 28.6 (CH_2), 47.6 (CH), 60.7 (CH_2), 113.2 (CH), 115.3 (CN), 119.3 (CH), 129.3 (CH), 139.3 (CH), 154.0 (CH=S), 160.2 (C=O). MS (*m/z* (%)): 398 (M^+, 100.0), 370 (80%). Anal. calcd. for $C_{20}H_{22}N_4O_3S$: C, 60.28; H, 5.57; N, 14.06. Found: C, 60.30; H, 5.58; N, 14.09%.

2-(5-Benzoyl-3-phenyl-1, 3, 4-thiadiazol-2(3H)-ylidene)-2-cyano-N-cyclohexylacetamide (**24e**): Color: Brown. Yield: 75%.

M.p.: 174-176 °C. FT-IR (KBr, ν, cm^{-1}): 1646 (C=O), 2171 (C=N), 3262 (NH). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.29-1.38 (m, 10H, H_2C), 3.58 (s, 1H, HC-NH), 6.50-7.07 (m, 5H, Ar-H), 7.45 (m, 3H, Ar-H), 7.81 (d, 2H, *J* = 3.1 Hz, Ar-H), 7.936 (s, 1H, HN D_2O-exchangable). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 23.3 (CH_3), 28.6 (CH_2), 47.6 (CH), 60.7 (CH_2), 113.2 (CH), 115.3 (CN), 116.3 (CH), 119.3 (CH), 129.3 (CH), 134.3 (CH), 146.0 (CH), 154.0 (CH=S), 160.2 (C=O), 183.0 (C=O). MS (*m/z* (%)): 430 (M^+, 100.0). Anal. calcd. for $C_{24}H_{22}N_4O_3S$: C, 66.96; H, 5.15; N, 13.01. Found: C, 66.98; H, 5.17; N, 13.06%.

3. Results and discussion

3.1. Chemistry

The reaction between cyclohexylamine (**1**) and ethyl cyanoacetate (**2**) without solvent under microwave irradiation afforded the corresponding 2-cyano-*N*-cyclohexyacetamide (**3**) in excellent yield as displayed in Scheme 1. The IR spectrum of the reaction product indicated three absorption bands at 3278 (NH), 2204 (C≡N), 1662 cm^{-1} (C=O). The mass spectrum exhibited a peak at *m/z* 166 attributable to the molecular ion of the acetamide **3**. The assignment is moreover assembled on the incidence of signals (δ 1.40-1.70 cyclohexyl, δ 3.30 CH_2, and δ 8.08 ppm NH) in ^1H NMR spectrum of the reaction product and its ^{13}C NMR exhibited signals at active methylene group at δ 27.3 ppm and carbonyl group at δ 171.2 ppm.

Performance of 2-cyano-*N*-cyclohexylacetamide (**3**) with the hydrazonoyl chloride **4** in ethanolic sodium ethoxide solution, it provides a single product for which the two possible structures **6** and **8** can be deliberated (Scheme 1). Nevertheless, elemental analysis and spectral data were in complete agreement with the aminopyrazole structure **6**. For instance, the IR spectrum of the aminopyrazole **6** displayed absorption bands at and 3280 cm^{-1} owing to amino group and exposed bands 1691 and 3409 cm^{-1} due to amide-NH and a carbonyl group, respectively. Additionally, its ^1H NMR spectrum exposed a signal at δ 6.52 and 8.05 ppm conforming to NH and NH_2 protons, respectively in adding to an aliphatic multiple at δ 1.39-1.49 ppm.

Consequently, the synthesis of some cyclohexyl-based 1,3,4-thiadiazole derivatives is tried. Subsequently, handling 2-cyano-*N*-cyclohexylacetamide (**3**) with phenyl isothiocyanate in dimethyl formamide, in presence of potassium hydroxide, at room temperature provided the non-isolable intermediate potssium salt **9** which was distorted into the consistent 2-cyano-*N*-cyclohexyl-3-mercapto-3-(phenylamino)acrylamide (**10**) upon handling with dilute hydrochloric acid as displayed in Scheme 2. The association of the latter product was recognized on the foundation of its elemental analysis and spectral analysis. For instance, its IR spectrum exposed a characteristic band at 3266 cm^{-1} owing to NH group and two strong absorption bands at 1670 and 2250 cm^{-1} to C=O and cyano group, respectively . Its ^1H NMR exposed signals at δ 1.37-1.52 ppm aliphatic multiplet corresponding to cyclohexyl protons, at δ 10.88 and 11.83 ppm due to NH and SH protons, respectively. Additionally, its mass spectrum exposed a peak at *m/z* 301 corresponding to its molecular ion. An acceptable mechanism for the synthesis of compound **10** is given in Scheme 2. Underneath microwave irradiation, compound **10** responds with bromo-1-phenylethanone derivatives **11a**,**b** in refluxing ethanol and in the occurrence of catalytic amount of triethylamine, to give the corresponding thiophene derivatives **13a** and **13b** (Scheme 2). The ^1H NMR spectrum of compound **13a** exposed a broad at δ 9.51 ppm D_2O-exchangeable signal owing to amide NH proton, furthermore, multiple at δ 6.46-7.01 ppm due to aromatic protons. Its mass spectrum demonstrated a molecular ion peak at *m/z* 419. The ^1H NMR spectrum of compound **13b** exposed a broad signal at δ 9.76 ppm (D_2O-exchangable) due to amide NH proton, in totaling to a multiplet signal at δ 7.05-7.38 ppm due to aromatic protons. Its mass spectrum demonstrated a molecular ion peak at *m/z* 497.

Correspondingly, compound **10** responds with ethyl bromoacetate (**14**) underneath forced microwave irradiation to give a single product identified as ethyl 4-(cyclohexylcarbamoyl)-3-amino-5-(phenylamino)thiophene-2-carboxylate (**16**) (Scheme 2). The previous product was apportioned on the basis of its elemental analysis and spectral data. Such as, its ^1H NMR spectrum revealed signal at δ 1.43-1.65 ppmdue to methyl protons, δ 4.183 ppm due methylene protons, in addition to a D_2O-exchangable signal at δ 6.61 ppm owing to NH_2 protons, a broad signal at δ 9.66 ppm (D_2O-exchangable) due to NH protons and a multiplet at δ 7.02-7.21 ppm owing to aromatic protons, respectively, Additionally, its mass spectrum revealed a peak at *m/z* 387 corresponding to its molecular ion.

In a comparable technique, compound **10** responds with chloroacetonitrile (**17**) to donate the corresponding 4-amino-5-cyano-*N*-cyclohexyl-2-(phenylamino)thiophene-3-carboxamide (**18**) (Scheme 3). The IR spectrum of the latter product presented strong carbonyl absorption band at 1650 cm^{-1}, nitrile band at 2250 cm^{-1} and NH and NH_2 band at 3428 and 3250 cm^{-1}, respectively. The ^1H NMR spectrum of the equivalent invention revealed a single signal exchangeable δ 6.60 ppm owing to amino protons, a broad D_2O-exchangable signal at δ 9.60 ppm due to NH proton and a multiplet signal at δ 7.02-7.21 ppm due aromatic protons. Its mass spectrum exposed a peak at *m/z* 340 corresponding to its molecular ion.

As soon as 2-cyano-*N*-cyclohexyl-3-mercapto-3-(phenylamino) acrylamide (**10**) was preserved with chloroacetone (**19**), it gave 2-cyano-*N*-cyclohexyl-2-(4-methyl-3-phenylthiazol-2(3*H*)-ylidene)acetamide (**21**) (Scheme 3). The mass spectrum of the previous product revealed a peak at *m/z* 339 consistent to its molecular ion. Its IR spectrum demonstrated absorption bands at 3419, 2163 and 1616 cm^{-1} owing to NH, nitrile and carbonyl group, respectively. The ^1H NMR spectrum of the matching products exposed a singlet signal at δ 1.03-1.09 ppm owing to aliphatic protons δ 2.08 ppm due to methyl protons, additionally to broad band D_2O-exchangable at δ 7.801 ppm due to NH protons and a multiplet at δ 7.41-7.51 ppm owing aromatic protons.

In a comparable way, reaction of the hydrazonoyl chloride **22a**-**e** with the intermediate potassium salt **9** further down the equivalent reaction condition furnished the afforded only one isolable product (as detected by thin layer chromotogrpahy) 1,3,4-thiadiazole derivatives (**24a**-**e**) and the further structures **25** and **26** were excluded based on the elemental and spectroscopic data of the reaction product (Scheme 4). The IR of compound **24a** displayed absorption band at 3340 cm^{-1} due to NH band, 2190 cm^{-1} due to nitrile band and strong carbonyl band at 1619 cm^{-1}, also its ^1H NMR spectrum revealed a signal at δ 1.79 ppm owing to CH_3 protons, δ 4.20 ppm due to CH_2 protons, in addition to multiplet singles at δ 6.40-7.21 ppm ppm owing to aromatic protons. Its mass spectrum revealed a peak at *m/z* 432 corresponding to its molecular ion. The extra probable structure **24a** was excluded on the basis of both analytical and spectral data.

3.2. Molecular orbital calculations

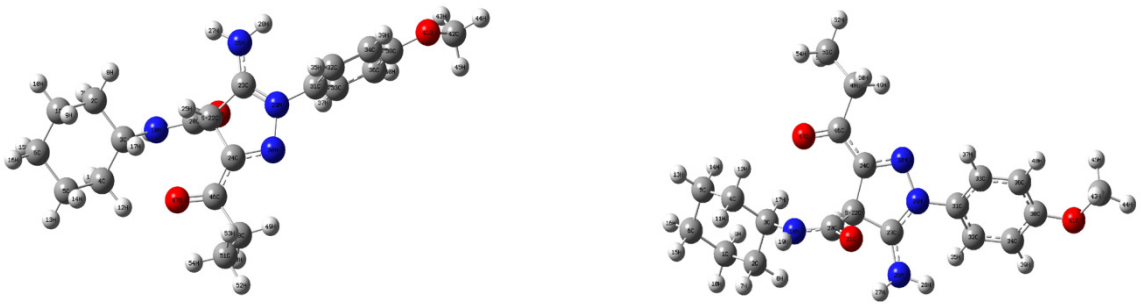
Optimization geometry of compounds **6** and **8** advanced at DFT (B3LYP) and HF hypothesis utilizing the Gaussian 09W program [30], which describe construction of pyrazole ethyl 4-(cyclohexylcarbamoyl)-5-amino-1-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate (**6**) instead of compound 4-cyano-*N*-cyclohexyl-3-ethoxy-2, 3-dihydro-1-(4-methoxyphenyl)-1*H*-pyrazole-5-carboxamide (**8**). Correspondingly theoretical calculation exhausting DFT calculation at the B3LYP level of theory and 6-31G (d) as a basis set as displayed in Table 1.

Table 1. Energetics of the ground state of compound **6** and **8** exhausting DFT (B3LYP/6-31G(d)).

Parameters	Compound 6		Compound 8	
E_T (au)	-1222.667		-1221.1528	
E_{HOMO} (au)	-0.21765		-0.20163	
E_{LOMO} (au)	-0.12886		-0.17188	
$E_g = E_{LOMO} - E_{HOMO}$ (eV)	2.4161001		0.80953	
μ (D)	5.6949		6.5415	
Net charges (au)	N30	-0.250	N37	-0.400
	N29	-0.629	N27	-0.323
	N26	-0.726	C22	-0.037
	O47	-0.518	C23	0.033
	C31	0.292	C28	0.527
	C23	0.635	N18	-0.635
	C22	0.334	O29	-0.496
	C24	0.201	C25	0.103
	N18	-0.636	N26	-0.246

Table 2. Structural parameters of compound **6** calculated using the B3LYP level and HF.

Parameters	Bond length (Å)		Parameters	Bond angles (°)	
	Calculated, HF/6-31G(d)	Experimental		Calculated, DFT/ B3LYP	Experimental
N30-N29	1.4029	1.43019	H19-N18-C20	113.0933	113.00599
N29-C23	1.3487	1.29388	N18-C20-O21	121.2687	121.51027
C23-C22	1.5088	1.51345	O21-C20-C22	119.1665	117.56467
C22-C24	1.5356	1.52672	N30-N29-C23	113.67825	111.92764
N30-C24	1.35967	1.36381	N29-C23-C22	109.0809	111.4882
C24-C46	1.42722	1.39801	N29-C23-N26	125.66977	126.01034
C46-O47	1.27715	1.26361	C22-C23-N26	125.17205	124.42526
C23-N26	1.36255	1.33060	C31-N29-N30	118.56020	117..5291
C20-N18	1.35801	1.33727	C31-N29-C23	127.7094	127.8572
C20-O21	1.26007	1.24062	H27-N26-H28	32.12128	116.73781
N29-C31	1.42657	1.42545	N30-C24-C46	122.11313	123.57956
O41-C42	1.45374	1.42878	O47-C46-C24	120.87440	121.10727



HF DFT

Figure 2. Optimized geometry, numbering system and atomic orbital of the frontier molecular orbital of compound **6** utilizing HF and DFT (B3LYP/6-31G(d).

The two *p*-isoelectronic structures **6** and **8** are dissimilar in order of stability, despite the fact 1*H*-pyrazole **6** appears an additional stable than pyrazole **8** by 1.5142 eV (≈ 950.175 kcal). Beginning the calculations of the energy gap, E_g, which calculate the chemical activity, pyrazole **6** was established to be extra reactive than amino pyrazole **8** by 37.048 kcal. Also ,The polarity or charge separation over the molecule,which is measured through the dipole moment μ, exhibited that μ of pyrazole **6** < μ of pyrazole **8** by 0.8466 Debye as displayed in Figure 2.

3.2.1. Geometry optimization of the compound 6

Complete geometry optimization of compound **6** was accomplished at DFT (B3LYP/6-31G(d)) and HF/6-31G(d) level of theory. Lowest potential energy surfaces for the optimized structure was checked as on the by frequency calculations. An opinion of the optimized structure and its atoms numbering are displayed in Figure 2. The bond distances and angles designated are scheduled in Table 2. The optimized geometry is associated with the crystallographic data of *N*-aryl pyrazoles [25-28]. The overall energy minimum of 3-amino-*N*-cyclohexyl-5-ethoxy-2, 3-dihydro-2-(4-methoxyphenyl)-1*H*-pyrazole-4-carboxamide (**6**) is -1222.6679 Hartree (-3.2×10^5 kcal/mol) with Dipole moment = 5.6949 Debye and -1214.8860 Hartree (-3.1×10^5 kcal/mol) with Dipole moment = 6.3747 Debye as measured through DFT/B3LYP and HF, respectively. The optimization studies that the molecule be appropriate to C_1 symmetry point group. It is well known that bond lengths and angles assumed at DFT/B3LYP/6-31G level of theory are regularly more exact than HF owing to the inclusion of electron correlation. On the contrary, in the present study, it was found that DFT(B3LYP/6-31G(d) technique associates well for the molecular parameters comparing with HF procedure (Table 2). Improved promise between the calculated bond lengths of compound **6** and the experimental data of *N*-aryl pyrazoles is found, subsequently the largest difference is originate to be 00978 Å and 0.01354 Å as designed at DFT/B3LYP(d) and HF, respectively. Additionally, the bond angles difference 0.584-4.012 for HF and 0.43944-14.52214 as displayed in Table 2.

3.2.2. Frontier molecular orbitals of compound 6

Frontier molecular orbital (FMO) is a influential guiding approach in the electrical and optical properties, in addition to UV-Vis spectra and chemical reactions. The HOMO and LUMO are actual important parameters used in quantum chemistry.

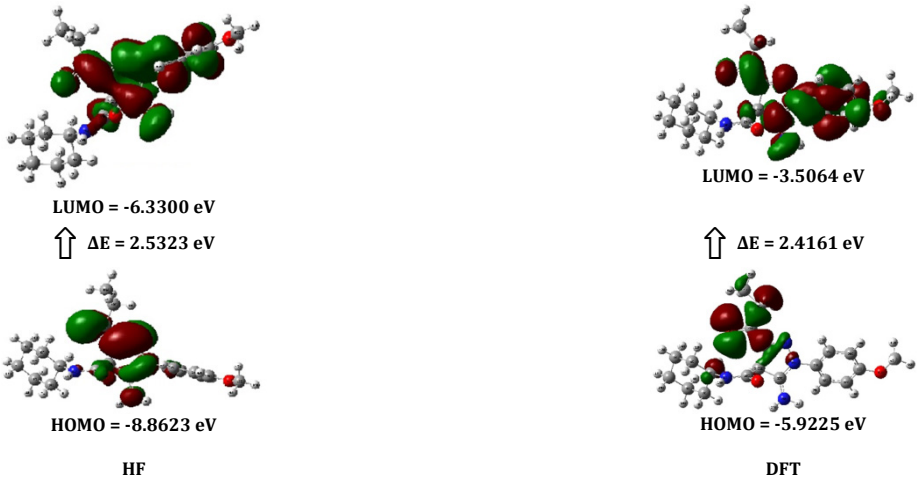


Figure 3. Gap energy (HOMO-LUMO) (eV) are calculated for compound **6** using HF and DFT.

Constructed on their characteristics, it can be indicated how a molecule would interact with other molecules. The HOMO orbitals can be considered as an electron donor group, while the LUMO orbitals as free sites capable to accept them. Due to the interaction between these orbitals, π-π* transition, with respect to the molecular orbital theory [33,34]. Energy of the HOMO orbitals can be directly linked to the ionization potential, whereas the LUMO orbital energy can be associated with the electron affinity. The difference between the orbital energies of HOMO and LUMO is referred to as energy gap, which is an important parameter that can determine the reactivity or stability of molecules. The energy gap between HOMOs and LUMOs associated to the biological activity of the molecule [35]. Moreover, it helps in characterizing the chemical reactivity and kinetic stability of the molecule. A large energy gap between HOMO-LUMO represents the high kinetic stability [36]. Figure 3 indications that the distributions and energy levels of the optimized compound **6** exhausting DFT (B3LYP/6-31G (d)) and HF/6-31G(d) possesses a dipole moment (5.6949 D) and (6.3747 D), respectively, and HOMO and LUMO energy gap of 2.4161 eV and 2.5323 eV which designates its extraordinary reactivity to cooperate with the surrounding media, and worthy permanence for this compound.

4. Conclusion

Herein, we report the synthesis of a variety of fused heterocyclic systems, consolidating cyclohexyl moiety via the reaction of 2-cyano-*N*-cyclohexylacetamide with phenyl isothiocyanate to afford the corresponding fused heterocycles utilizing conventional procedures and microwave irradiation techniques. Optimized molecular structure, bond distance, bond angles and difference of energy (HOMO-LUMO) have been investigated by DFT/B3LYP and HF approaches combined with 6-31G(d) basis set. Comprehensive theoretical and experimental structural studies pyrazole ethyl 4-(cyclo hexylcarbamoyl)-5-amino-1-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate have been carried out by elemental analysis, FT-IR, ^{1}H NMR, and Mass spectroscopy.

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