Regioselective synthesis and DFT study of novel fused heterocyclic utilizing Thermal heating and Microwave Irradiation

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Síntesis regioselectiva y estudio DFT (teoría del funcional de la densidad) de nuevos sistemas heterocíclicos fundidos que utilizan irradiación térmica e irradiación por microondas

Síntesi regioselectiva i estudi DFT (teoria del funcional de la densitat) de nous sistemes heterocíclics fosos que utilitzen irradiació tèrmica i irradiació per microones

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SUMMARY

Regioselective facile synthesis of innovative heterocycles from the reaction of 2-cyano-*N*-cyclohexylacetamide (**3**) with *N, N*- dimethylformamide dimethyl acetal (*DMF-DMA*) to afford (*E*)-2-cyano-*N*-cyclohexyl-3-(dimethylamino)acrylamide (**4**) under microwave irradiation. Enaminonitrile **4** reacts with hydrazine derivatives affords the corresponding pyrazole derivatives **5a-c**, furthermore the behavior of enaminone **4** reacts with guanidine to give the corresponding 2,4 diaminopyrimidine derivative (**7**). Moreover (*E*)-2-cyano-N-cyclohexyl-3-(dimethylamino) acrylamide (**4**) reacts with amino pyrazoles **8a-f**, 1,2,4-aminotriazole (**11**) and 2-aminobenzimidazole (**13**) to afford the corresponding pyrazolo[1,5-*a*]pyrimidine **9a-f**, and triazolo[4,3-*a*]pyrimidine **12,** pyrimido[1,2-*a*]benzimdazole **14**; respectively. Density functional theory calculations at the B3LYP/6-31G (d) levels of theory have been carried out to investigate the equilibrium geometry of the novel fused pyrazoles **5a** and **9a.** Moreover, the total energy, the energy of the HOMO and LUMO and Mulliken atomic charges were considered. Additionally, the measurements of their interactions with hydrazine hydrate to form fused pyrazoles **5a** and **9a** have been calculated. Also, comprehensive theoretical and experimental structural studies of 7-amino-*N*-cyclohexyl-2-methyl-3-phenylpyrazole[1,5-*a*]pyrimidine-6-carboxamide **(9a)** have been carried out by elemental analysis, FTIR, ^{1}H NMR and Mass. Optimized molecular structure and harmonic vibrational frequencies have been reconnoitered by DFT/B3LYP and HF methods combined with 6-31G(d) basis set.

Keywords: Enaminonitrile; cyclohexylamine; aminopyrazole; aminopyrimidine; triazole [4,3-*a*] pyrimidine; pyrazolo[1,5-*a*]pyrimidine; pyrimido[1,2-*a*] benzimidazole; DFT calculations.

RESUMEN

Síntesis regioselectiva simple de los heterociclos innovadores de la reacción del 2-ciano-N-ciclohexilacetamida (**3**) con N, N- dimetilformamida dimetil acetal (DMF-DMA) para conseguir (E)-2-ciano-N-ciclohexil-3-(dimetilamino) acrilamida (**4**) en una irradiación por microondas. La enaminonitrilo **4** reacciona con los derivados de hidracina para dar los correspondientes derivados de pirazol **5a-c,** de forma que la enaminona **4** reacciona con la guanidina para dar el correspondiente derivado 2,4 diaminopirimidina **(7**). Además, la (E)-2-ciano-N-ciclohexil-3-(dimetilamino) acrilamida (**4**) reacciona con los aminopirazoles **8a-f,** 1,2,4-aminotriazol (**11**) y 2-aminobenzimidazol (**13**) para obtener el correspondiente pirazol[1,5-a]pirimidina **9a-f**, el triazol[4,3-a] pirimidina **12**, y el pirimido[1,2-a]bencimidazol **14**, respectivamente. Se han llevado a cabo cálculos de

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la teoría del funcional de la densidad a niveles teóricos de B3LYP/6-31G (d) para investigar la geometría del equilibrio de los nuevos pirazoles fundidos **5a** y **9a.** Además se han tenido en cuenta la energía total, la energía del HOMO y LUMO y las cargas atómicas de Mulliken. Adicionalmente, se han calculado las mediciones de sus interacciones con hidratos de hidracina para formar pirazoles fundidos **5a** y **9a**. Asimismo también se han realizado detallados estudios estructurales, teóricos y experimentales, del 7-amino-N-ciclohexil-2-metil-3-fenilpirazol[1,5-a] pirimidina-6-carboxamida (**9a**) mediante análisis elemental, FTIR, 1H NMR y espectroscopia de masas. La estructura molecular optimizada y las frecuencias vibracionales armónicas han sido exploradas mediante los métodos DFT/B3LYP y HF en combinación con el equipo de base 6-31G(d).

Palabras clave: Enaminonitrilo; ciclohexilamina; aminopirazol; aminopirimidina; triazol [4,3-a] pirimidina; pirazol[1,5-a]pirimidina; pirimido[1,2-a]bencimidazol;, cálculos de la DFT.

RESUM

Síntesi regioselectiva simple dels heterocíclics innovadors de la reacció del 2-ciano-N-ciclohexilacetamida (**3**) amb N, N- dimetilformamida dimetil acetal(DMF-DMA) per aconseguir (E)-2-ciano-N-ciclohexil-3-(dimetilamino)acrilamida (**4**) en una irradiació per microones. La enaminonitrilo **4** reacciona amb els derivats de la hidrazina per donar resultat als corresponents derivats de pirazol **5a-c,** de forma que la enaminona **4** reacciona amb la guanidina per obtenir el corresponent derivat 2,4 diaminopirimidina (**7**). D'altra banda, la (E)-2-ciano-N-ciclohexil-3-(dimetilamino) acrilamida (**4**) reacciona amb els aminopirazoles **8a-f**, 1,2,4-aminotriazol (**11**) i 2-aminobenzimidazol (**13**) per obtenir el corresponent pirazol[1,5-a]pirimidina **9a-f**, el triazol[4,3-a]pirimidina **12**, i el pirimido[1,2-a]bencimidazol **14** respectivament. S'han portat a terme càlculs de la teoria del funcional de la densitat a nivells teòrics del B3LYP/6-31G (d) per investigar la geometria del equilibri dels nous pirazols fosos **5a** i **9a**. A més a més s'ha tingut en compte la energia total, la energia del HOMO i LUMO i les carreges atòmiques de Mulliken. Addicionalment, s'han calculat les mesures de les seves interaccions amb hidrats de hidrazina per formar els pirazols fosos **5a** i **9a**. Al mateix temps també s'han realitzat estudis estructurals detallats, teòrics i experimentals, del 7-amino-N-ciclohexil-2-metil-3-fenil-pirazol[1,5-a]pirimidina-6-carboxamida (9a) per mitjà del anàlisi elemental, FTIR, 1H NMR i la espectroscòpia de massa. La estructura molecular optimitzada i les freqüències vibracionals harmòniques han sigut explorades per mitjà dels mètodes DFT/B3LYP i HF en combinació amb l'equip de base 6-31G(d).

Paraules clau: Enaminonitrilo; ciclohexilamina; aminopirazol; aminopirimidina; triazol [4,3-a] pirimidina; pirazol[1,5-a]pirimidina; pirimido[1,2-a]bencimidazol;, càlculs de la DFT.

INTRODUCTION

The class of cyclohexylamine derivatives excludes acetylcholinesterase inhibitors[1, 2], activators of dopamine receptors in the CNS[3], and highly active-opioid analgesics[4]. The innovation of the psychotomimetic action of the recognized analgesic drug phencyclidine[5] has expanded investigations devoted to the synthesis and pharmacological characterization of numerous derivatives of cyclohexylamine[6-10]. Cyanoacetamide derivatives are extremely reactive, polyfunctional compounds that possess both electrophilic and nucleophilic centers. Cyanoacetamide is accomplished of dimerization once heated in alkaline medium. Two of the nucleophilic centers in cyanoacetamides are localized on the NH and the C-2 positions with a reactivity order C-2 > NH. Two electrophilic positions are accompanying with the C-1 and C-3 positions with reactivity order C-3 > C-1 (**Figure. 1**)[11-13]. Cyanoacetamide derivatives are commonly used as active synthons for the syntheses of many open-chain systems and polysubstituted heterocyclic compounds[14-15]. Cyanoacetamide chemical properties have been used to design various heterocyclic moieties with different ring sizes. The occurrence of two electron-withdrawing groups' outcomes in the high activity of cyanoacetamides as *CH* acidic and the active methylene means they can cooperate in a variability of condensation and substitution reactions[16-19].

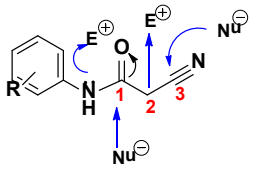


Figure 1. *Cyanoacetamide derivatives reactivity*

Moreover, their carbonyl and the cyano functional groups facilitate them to react with common reagents to form a variety of heterocyclic compounds such as thiophene[20], pyrazole[17], thiazole[17-19], 1,3-dithiazole, 1,3-dithiane[13], pyridine[13-17], chromene and coumarin derivatives[13-15]. Furthermore, cyanoacetamide derivatives were exploited as key precursors for the synthesis of polycondensed heterocyclic compounds such as pyrazolo [1,5-*a*]pyrimidine[13], pyrano[3,2-*g*]-chromene[13], pyrazolo [3,4-*b*] pyrazines[20] and thiazolo[3,2-a]pyridines[21]. Upon a comprehensive survey of the methods for the preparation and chemical reactivity of cyanoacetamide derivatives, we found that the synthesis of cyanoacetamides could be carried out in several ways. The most adaptable and commonly used preparative method is the acylation of aromatic or heterocyclic amines with ethyl cyanoacetate under various reaction conditions[17, 22]. The enaminonitrile (*E*)-2-cyano-*N*-cyclohexyl-3-(dimethylamino) acrylamide (**4**) hasn't described in literature hitherto, which used for the synthesis of heterocyclic compounds pendant with-*N*-cyclohexyl amide moiety of expected biological activity[23-25]. Moreover, microwave irradiation has been recently demonstrated its utility as an energy source to improve yields and/or save reaction

condition, especially in the field of heterocyclic synthesis[26-28]. Our concern of research designates simple and efficient route for the synthesis of novel pyrimidine carboxamide, pyrazolo pyrimidine, triazole pyrimidine carboxamide, benzimidazole pyrimidine derivatives. derivatives interacting cyclohexyl moiety utilizing microwave irradiation. Density functional theory (DFT) has been improved in theoretical modeling. Different computational techniques can predict the chemical and physical properties of biological and chemical systems[29-35]. Herein, we executed theoretical studies on the most encouraging compounds **5a** and **9a** utilizing DFT/B3LYP/6-31G (d) method.

EXPERIMENTAL

Materials and methods

All melting points were measured with a Gallenkamp melting point apparatus. IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. 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*) using TMS as an internal standard. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Micro analytical Center of Cairo University, Giza, Egypt. Microwave experiments were carried out using CEM Discover ™ microwave apparatus.

Material and reagents

Cyclohexylamine, ethyl cyanoacetate, dimethylformamide dimethyl acetal (*DMF-DMA*), hydrazine hydrate, phenyl hydrazine, triethylamine, 2-amino benzimidazole, aminopyrazole, and aminotriazole were purchased from Aldrich Chemical CO. Ethanol, and pyridine, toluene, THF, piperidine purchased from Aldrich Chemical CO. Methanol, isopropyl alcohol, petroleum ether; chloroform where BDH reagents were purchased from EL-Nasr Pharmaceutical and Chemical Co. (ADWIC), Egypt.

Synthesis of (E)-2-cyano-N-cyclohexyl-3- (dimethylamino) acrylamide (4)

To a solution of 2-cyano-*N*-cyclohexylacetamide[36-37] (**3**) (10g, 10mmol) in dry toluene or without solvent was added dimethylformamide-dimethyl acetal (*DMF-DMA*) (10ml,12 mmol) and the mixture was mixed in an HP-500 Plus process vessel. The vessel was capped properly and irradiated by microwaves under pressurized conditions (17.2 bar, 110°C) for 10 min. The excess DMF-DMA was evaporated *in vacuo* and the residue was dissolved in diethylether (50 ml) and dried over $MgSO_4$. After evaporation of the solvent the subsequent solid was recrystallized in ethanol to give **(*E*)-2-cyano-*N*-cyclohexyl-3-(dimethylamino)acrylamide (4)** with yield 75% ; m.p 140-142°C, ; IR (KBr) ν_{max}/cm^{-1}: 1656 (C=O), 3342 (NH), 2186 (C=N), cm^{-1}; ^{1}H NMR (DMSO d_6): 1.4-1.7 (m, 10H, H_2C), 3.09(s, 6H, H_3CH), 3.51(s,1H, *H*C-NH), 6.58(d, 1H, *H*C, *J*=2.7Hz), 7.66(s, 1H, *H*N D_2Oexchangeable) ; ^{13}C NMR (75MHz, DMSO-*d6*) δ 22.9 (*C*H_2), 28(*C*H_2), 33.8 (*C*H_2), 42.3(*C*H_3), 46.9(*C*H), 98.8 (*C*H), 115.9 (*C*N), 156.1 (*C*H=), 159(*C*=O); MS *m/z* (%)123(M$^+$, 100.0%), 221(34.8%), 163 (16.4%), 53 (23.2%), Anal calcd $C_{12}H_{19}N_3O$ (221.13) : C, 65.13; H, 8.65; N,18.99 % ;Found: C,65.10; H, 8.68; N,19.03%;

Reactions of Enamonitrile 4 with hydrazine hydrate derivatives: General procedure

Thermal method: Enaminonitrile **4** (0.44g, 2mmol) in isopropyl alcohol (20ml), hydrazine hydrate 80% (0.2ml, 2mmol), phenyl hydrazine (0.2ml, l) and phenyl sulfahydrazine (0.344g, 2 mmol) was added. The resulting mixture was refluxed for 4h and observed by TLC and then allowed to cool the solid formed was filtered off and washed with ethanol and dried. Recrystallization from ethanol afforded the corresponding pyrazoles derivatives **5a-c.** ***Microwave method*:** To a solution of Enaminonitrile **4** (.44g , 2mmol) in isopropyl alcohol (20ml), hydrazine hydrate80%, (0.2ml, 2mmol), phenyl hydrazine (0.2ml,) and phenyl sulfa hydrazine (0.344 g, 2mmol) was added. The reaction mixture was mixed in a HP-500 Plus process vessel. The vessel was capped properly and irradiated by microwaves under pressurized conditions (17.2 bar, 130°C) for 20 min (examined by TLC), the cooled the solid formed was filtered off and washed by ethanol and dried. Recrystallization from ethanol afforded the corresponding pyrazoles derivatives **5a-c**

5-amino-*N*-cyclohexyl-1*H*-pyrazole-4-carboxamide (5a) yield 85 %; mp=214-216 °C ; IR (KBr) ν_{max}/cm^{-1}: 1646 (C=O), 3409(NH), 3336(NH_2) cm^{-1}; ^{1}H NMR (DMSO d_6): δ1.3-1.8(m, 10H, H_2C), 3.53(s, 1H, *H*C-NH), 6.37(s, 2H, H_2ND_2O-exchangable), 7.85 (s,1H, *H*ND_2O-exchangable),7.96 (s, 1H, *H*C),13.2 (s, 1H, *H*N D_2O-exchangable pyrazole), ^{13}CNMR(300MHz, DMSO-d_6) δ 22.9(*C*H_2), 28(*C*H_2), 33.8(*C*H_2), 47.1(*C*H), 114.5(*C*H_2), 144.6(*C*H), 154(*C*H=), 167.3 (*C*=O); MS *m/z* (%) 208 (M$^+$, 100.0%), 192 (54.2%), 127 (25.5%); Anal calcd $C_{10}H_{16}N_4O$ (208.26) C, 57.67; H, 7.74; N, 26.90; Found C, 57.70; H, 7.76; N, 26.88;

5-amino-*N*-cyclohexyl-1-phenyl-1*H*-pyrazole-4-carboxamide (5b) yield 80%; mp=240-242 °C ; IR (KBr) ν_{max}/cm^{-1}: 1646 (C=O), 3409 (NH), 3336 (NH_2), cm^{-1}; ^{1}H NMR (DMSO-d_6): δ1.3-1.8(m, 10H, H_2C), 3.53(s,1H, *H*C-NH), 6.37 (s,2H, H_2N-D_2O-exchangable), 7.48-7.54(m,5H, *H*Ars), 7.85 (s,1H, *H*N D_2O-exchangable), 7.96(s, 1H, *H*C);^{13}C NMR (300MHz- DMSO-*d6*) δ 22.9 (*C*H_2), 28 (*C*H_2), 33.8 (*C*H_2), 47.1 (*C*H), 120.2 (*C*H), 126.3 (*C*H), 129.3 (*C*H), 129.4 (*C*H), 139.7 (*C*H), 140.6 (*C*H=), 142 (*C*H=), 150.1 (*C*H=), 167.3 (*C*=O); MS *m/z* (%) 186 (M$^+$, 100.0%), 284 (27.5%), 241 (12.3%), 120(10.6%); Anal calcd $C_{16}H_{20}N_4O$ (284.36) C, 67.58; H, 7.09; N, 19.70; Found C, 67.63; H, 7.12; N, 19.76.

5-amino-*N*-cyclohexyl-1-phenylsulphone-1*H*-pyrazole-4-carboxamide (5c) yield 80%; mp=200-202 °C ; IR (KBr) ν_{max}/cm^{-1}: 1646 (C=O), 3409 (NH), 3359 (NH_2) cm^{-1}; ^{1}H NMR (DMSO- d_6): δ1.3-1.8(m, 10H, H_2C), 3.53(s,1H,*H*C-NH) , 6.42

(s, 2H, H_2ND_2O-exchangable), 7.54(m, 3H, *H*CH), 7.66(s, 1H, *H*CH) 7.85 (s, 1H, *H*NH), 7.93(d, 2H, *HC*, *J*=6Hz);^{13}C NMR (300MHz- DMSO-d_6)**:**δ 22.9 (CH_2), 28 (CH_2), 33.8 (CH_2), 47.1 (*C*H), 128.3 (*C*H), 129.8 (*C*H), 133.2 (*C*H), 133.8 (*C*H), 137.9 (*C*H), 139.4 (CH_2), 167.3(*C*=O); MS *m/z* (%) 250 (M^+, 100.0%), 348 (30.2%) ; Anal calcd $C_{16}H_{20}N_4O_3S$ (348.42) C, 55.16; H, 5.79; N, 16.08; S, 9.20 Found C, 55.21; H, 5.76; N, 16.0; S, 9.24.

Reactivity of (E)-2-cyano-N-cyclohexyl-3-(dimethylamino) acrylamide (4) towards guanidine nitrate

Thermal method: To a mixture of Enaminonitrile **4** (0.44g, 2 mmol) and the guanidine nitrate (0.222g, 2.0 mol), dissolved in isopropyl alcohol (30ml) anhydrous potassium carbonate (0.552g, 4 mmol) was added. The reaction mixture was refluxed for 6h and observed by TLC and then allowed to cool at room temperature and diluted with water (20ml), and washed with water and dried. Recrystallization from ethanol afforded compound **7**

Microwave method: Enaminonitrile (0.44g, 2 mmol) and the guanidine nitrate (0.222g, 2.3 mol), in isopropyl alcohol (30 ml) anhydrous potassium carbonate (0.552 g, 4 mmol) was added. The reaction mixture was mixed in an HP-500 Plus process vessel. The vessel was capped properly and irradiated by microwaves under pressurized conditions (17.2 bar, 130°C) for a specified 20 minutes (examined by TLC), and left to cool at room temperature and pour on ice so the solid product was designed and then collected by filtration and washed with water and dried. Recrystallization from ethanol to afforded **2,4-diamino-*N*-cyclohexylpyrimidine-5-carboxamide** (**7**) in 60% yield ; m.p =216-217 ° C; IR KBr) ν_{max}/cm^{-1}: 1650 (C=O), 3679 (NH), 3347 (NH_2), cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.4-1.7 (m, 10H, H_2CH_2), 3.53(s, 1H,HC-NH) , 5.32 (s, 2H, H_2N D_2O-exchangable) 6.21(s,2H, H_2N D_2O-exchangable), 7.9 (s,1H, *H*N D_2O-exchangable), 8.14(s, 1H, *H*C); ^{13}C NMR (300MHz, DMSO-*d6*) δ 22.9(CH_2), 28(CH_2), 33.8(CH_2), 47.1(*C*H), 102.1(*C*H), 157.2 (*C*H=), 160.5 (*C*H=), 162.9 (*C*=N), 167.3 (C=O) ; MS *m/z* (%) 235 (M^+, 100.0%), 219 (45.3%), 203 (30.5%) ;Anal calcd $C_{11}H_{17}N_5O$ (235.29) C, 56.15; H, 7.28; N, 29.77; Found C, 56.19; H, 7.30; N, 29.80.

Reaction of Enaminonitrile 4 with heterocyclic amine 9(a-f), 12 and 14:

Thermal method: Enaminonitrile 4 (0.44g, 2mmol) and the appropriate heterocyclic amine **9** (**a**-**f**), **12** and **14** (2 mmol) in pyridine (15 ml).The reaction mixture was refluxed for 4h, then left to cool at room temperature .the precipitated product was filtered off, washed with ethanol dried and finally recrystallized from ethanol to afford the corresponding products **9**(**a**-**f**), **12** and **14**; respectively.

Microwave method: Mixture of compound **4** (0.44g, 2mmol) and the appropriate heterocyclic amine **9** (**a**-**f**), **12** and **14** (2mmol) in pyridine (15ml), the reaction mixture was mixed in a HP-500 Plus process vessel. The vessel was capped properly and irradiated by microwaves under pressurized conditions (17.2 bar, 130°C) for a given 20 min (examined by TLC), and left to cool at room temperature the precipitated product was filtered off , washed with ethanol dried and finally recrystallised from ethanol to afford the corresponding products **9** (**a**-**f**) ,**12** and **14**; respectively.

7-amino-N-cyclohexyl-2-methyl-3-phenylpyrazolo [1,5-a]pyrimidine-6-carboxamide (9a): yield 70% mp =212-214 °C ; IR (KBr) ν_{max}/cm^{-1}: 1648 (C=O), 3340 (NH), 3262(NH_2), cm^{-1}; ^{1}HNMR (DMSO d_6): δ1.3-1.8 (m, 10H, H_2C), 2.79(s,3H, H_3C), 3.53(s, 1H, *H*C-NH), 7.32-7.48(m, 5H, *H*Ars), 7.91 (s,1H, *H*N) 8.42 (s, 2H, H_2ND_2O-exchangable), 9.21(s, 1H, *H*C); ^{13}C NMR (300MHz-DMSO-d_6)**:** δ 17.2 (CH_3), 22.9 (CH_2), 28 (CH_2), 33.8 (CH_2), 47.1 (*C*H), 112.7 (*C*H), 125.7(*C*H), 127.5 (*C*H), 128.8 (*C*H), 129.3 (*C*H), 133.2 (*C*H), 136.4 (*C*H), 138.4 (*C*H), 161.4 (*C*H=), 167.3 (*C*=O), 169 (*C*H=); MS *m/z* (%) 349 (M^+, 100.0%), 272 (25.7%); Anal calcd $C_{20}H_{23}N_5O$ (349.43) C, 68.74; H, 6.63; N, 20.04; Found C, 68.78; H, 6.66; N, 20.06;

7-amino-N-cyclohexyl-3-methylpyrazolo[1,5-a] pyrimidine-6-carboxamide (9b): yield 85%; mp= 252-254°C ; IR (KBr) ν_{max}/cm^{-1}: 1652 (C=O), 3340(NH), 3262(NH_2)cm^{-1}; ^{1}H NMR(DMSO-d_6): δ1.3-1.8(m, 10H, H_2C), 2.79(s, 3H, H_3C), 3.53(s, 1H, *H*C-NH), 6.06 (s, 1H, *H*C), 7.98 (s, 1H, *H*N), 8.42(s, 2H, H_2ND_2O-exchangable), 9.05(s, 1H, *H*C); ^{13}C NMR (300MHz-DMSOd_6)**:** δ 11.1 (CH_3), 22.9 (CH_2), 28 (CH_2), 33.8 (CH_2), 47.1 (*C*H), 112.7 (*C*H), 115.6 (*C*H), 132.7 (*C*H), 132.9 (*C*H), 161.4 (*C*H=), 167.3 (*C*=O), 171.2 (*C*H=); MS *m/z* (%)273 (M^+, 100.0%), 257 (26.9%) ; Anal calcd $C_{14}H_{19}N_5O$ (273.33**)** C, 61.52; H, 7.01; N, 25.62; Found C, 61.56; H, 7.05; N, 25.67;

7-amino-3-(aza-2-chlorophenyl)-*N*-cyclohexylpyrazolo[1,5-*a*]pyrimidine-6-carboxamide (9c): yield 75%; mp= 230-231 °C ; IR (KBr) ν_{max}/cm^{-1}: 1652 (C=O), 3340(NH), 3262(NH_2) cm^{-1}; ^{1}H NMR (DMSO -d_6): δ 1.3-1.84 (m, 10H, H_2C), 3.59 (s, 1H, *H*C-NH), 6.60 (s, 1H, *H*C), 7.18 (m, 1H, *H*C), 7.31 (t, 1H, *H*C, *J*=6Hz), 7.40 (d, 1H, *H*C, *J*=10.2Hz), 7.81(s, 1H, *H*N), 7.84 (d, 1H, *HC*, *J*=6Hz), 8.74 (s, 2H, H_2N D_2O-exchangable), 8.99 (s, 1H, *HC*); ^{13}C NMR (300MHz- DMSO*d6*)**:** δ 22.9 (CH_2), 33.8 (CH_2), 47.1 (*C*H), 105 (*C*H), 112.7 (*C*H), 126.9 (*C*H), 128.1(*C*H), 128.9 (*C*H), 129 (*C*H),133 (*C*H), 134.3 (*C*H), 161.4 (*C*H=), 167.3(*C*=O); MS *m/z* (%) 397 (M^+, 100.0%), 399 (32.5%), 120(18.7%);Anal calcd $C_{19}H_{20}ClN_7O$ (397.86**)** C, 57.36; H, 5.07, Cl, 8.91; N, 24.64**;** ; Found C, 57.32; H, 5.11; Cl, 8.89; N, 24.67;

7-amino-3-(4-bromophenyl)-*N*-cyclohexylpyrazolo[1,5-*a*]pyrimidine-6-carboxamide (9d): yield 71% mp=<300 °C ; IR (KBr) ν_{max}/cm^{-1}: 1652 (C=O), 3340 (NH), 3262(NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ1.3-1.84 (m, 10H, H_2C), 3.59(s, 1H, *H*C-NH), 7.37(d,2H, *HC*, *J*=6.1Hz), 7.49 (d, 2H, *HC*,), 8.03(s, 1H, *H*N), 8.40(d, 1H, *HC*, *J*=8.6Hz), 8.74(s, 2H, H_2ND_2O- exchangable), 9.06 (s, 1H, *HC*);^{13}C NMR(300MHz-DMSO-d_6)**:** δ 22.9 (CH_2), 33.8 (CH_2), 47.1 (*C*H), 97(*C*H) , 112.7 (*C*H), 123.1 (*C*H), 129.7 (*C*H), 129.7 (*C*H), 130.7 (*C*H), 132.2 (*C*H), 135.4 (*C*H), 161.4 (*C*H=), 168 (*C*=O), 169

(*C*H=); MS *m/z* (%) 413 (M^+, 100.0%), 415 (97.3%), 67 (38.3%) ; Anal calcd $C_{19}H_{20}BrN_5O$ (414.3**)** C, 55.08; H, 4.87; Br, 19.29; N, 16.90; Found C, 55.11; H, 4.89; Br, 19.33; N, 16.93;

7-amino-*N*-cyclohexyl-3-(4-methoxyphenyl) pyrazolo[1,5-*a*]pyrimidine-6-carboxamide (9e): yield 75% mp= <300 °C ; IR (KBr) ν_{max}/cm^{-1}: 1652 (C=O), 3340 (NH), 3262 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ1.3-1.84 (m, 10H, H_2C), 3.59(s, 1H, *H*C-NH), 3.73(s, 3H, H_3OC),6.83 (d, 2H, *H*C, *J*=6.1Hz), 7.37 (d, 2H, *H*C, *J*=6.1Hz), 8.09 (s, 1H, *H*N), 8.40 (d, 1H, *H*C, *J*=12.1Hz), 8.74 (s, 2H, H_2ND_2O-exchangable), 9.05(s, 1H, *H*C); ^{13}C NMR (300MHz-DMSO*d6*)**:** δ 22.9 (*C*H_2), 28 (*C*H_2), 33.8 (*C*H_2), 47.1 (*C*H), 55.9 (*C*H_3),97 (*C*H), 112.7 (*C*H), 114.8 (*C*H), 128.5 (*C*H), 128.7 (*C*H), 130.4 (*C*H), 130.8(*C*H), 160.7(*C*H), 161.4(*C*H=), 169.3(*C*=O),171(*C*H=); MS *m/z* (%) 365.14 (M^+, 100.0%), 366 (22%); Anal calcd $C_{20}H_{23}N_5O_2$ (365.43**)** C, 65.73; H, 6.34; N, 19.16; Found C, 65.76; H, 6.35; N, 19.19;

7-amino-2-bromo-*N*-cyclohexyl-3-phenylpyrazolo[1,5-*a*]pyrimidine-6-carboxamide (9f): yield 75%; mp= 224 °C ; IR (KBr) ν_{max}/cm^{-1}: 1652 (C=O), 3340(NH), 3262(NH_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.3-1.84 (m, 10H, H_2C), 3.59(s,1H, *H*C-NH), 7.22(m, 1H, *H*C), 7.32(d, 2H, *H*C, *J*=6.1Hz), 7.84(d, 2H, *H*C, *J*=6.1Hz), 7.91(s, 1H, *H*N), 8.78 (s, 2H, H_2ND_2O-exchangable), 9.01(s, 1H, *H*C); ^{13}C NMR (300MHz-DMSO-d_6)**:** δ 22.9(*C*H_2), 28(*C*H_2), 33.8(*C*H_2), 47.1(*C*H), 112.7(*C*H), 117.1(*C*H), 127.5(*C*H),128.8(*C*H),129.3(*C*H),129.8(*C*H),131(*C*H), 136.4(*C*H), 162.1(*C*H=), 169(*C*=O), 172(*C*H=); MS *m/z* (%) 413.09 (M^+, 100.0%), 315 (97.3%); Anal calcd $C_{19}H_{20}BrN_5O$ (414.3**)** C, 55.08; H, 4.87; Br, 19.29; N, 16.90**;** Found C, 55.11; H, 4.89; Br, 19.33; N, 16.88;

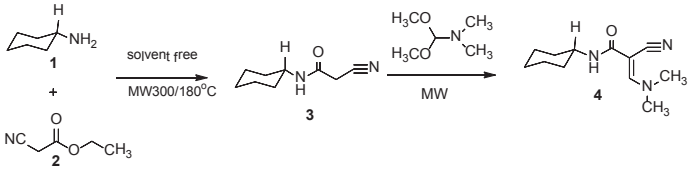
5-amino-*N*-cyclohexyl-[1,2,4]triazolo[4,3-*a*] pyrimidine-6-carboxamide 12: yield 70% mp = 290-292 °C ; IR (KBr) ν_{max}/cm^{-1}: 1662 (C=O), 3430 (NH), 3274 (NH_2) cm^{-1}; ^1HNMR (DMSO-d_6)**:** δ1.3-1.8 (m, 10H, H_2C), 3.53(s, 1H, *H*C-NH), 7.91(s, 1H, *H*N), 8.22(s, 1H, *H*C), 8.46 (s, 2H, H_2ND_2O-exchangable), 9.26 (s, 1H, *H*CH); ^{13}C NMR(300MHz, DMSO-d_6)**:** δ 22.9 (*C*H_2), 28 (*C*H_2), 33.8 (*C*H_2), 47.1(*C*H), 112.7 (*C*H), 139.7 (*C*H), 152.8 (*C*H=), 160.4 (*C*H=), 168.3 (*C*=O), 170(*C*H); MS *m/z* (%) 162 (M^+, 100.0%), 260 (95%), 178 (63.5%), ; Anal calcd $C_{12}H_{16}N_6O$ (309.37**)** C, 55.37; H, 6.20; N, 32.29; Found C, 55.34; H, 6.25; N, 32.33;

4-amino-*N*-cyclohexyl-4,6-dihydropyrimido[1,2-*b*]indazole-3-carboxamide 14: 75% yield mp = <300 °C ; IR (KBr) ν_{max}/cm^{-1}: 1656 (C=O), 3347(NH), 3266 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.3-1.8 (m, 10H, H_2C), 3.8(s, 1H, *H*CH-NH), 7.36 (t, 2H, CH, *J*=2.7Hz), 7.75(d, 2H, *H*C, *J*=2.8Hz), 8.04 (s, 1H, *H*N), 8.44 (s, 2H, H_2ND_2O-exchangable), 9.26 (s, 1H, *H*C); ^{13}CNMR (300MHz, DMSO-d_6)**:** δ 22.9 (*C*H_2), 28 (*C*H_2), 33.8 (*C*H_2), 47.1 (*C*H), 112.7 (*C*H) ,115.3 (*C*H), 123 (*C*H), 135.2 (*C*H), 138.9 (*C*H), 150 (*C*H=), 168.3 (*C*=O), 169 (*C*H=); MS *m/z* (%) 309 (M^+, 100.0%), 211(79.4%) ,310(26.6%), Anal calcd $C_{17}H_{19}N_5O$ (309.37) C, 66.00; H, 6.19; N, 22.64; Found C, 66.09; H, 6.22; N, 22.68;

RESULTS AND DISCUSSION

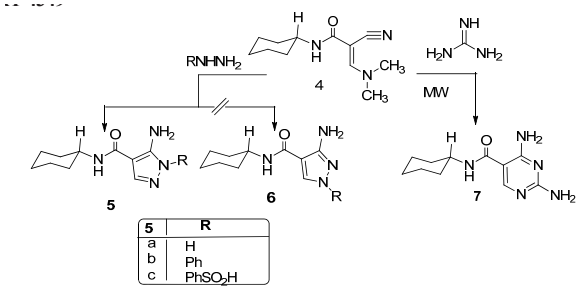
Chemistry

The reaction between cyclohexylamine and ethyl cyanoacetate without solvent under microwave irradiation afforded the corresponding 2-cyano-*N*-cyclohexyacetamide (**3**) in excellent yield. Solvent-free synthesis of (*E*)-2-cyano-*N*-cyclohexyl-3-(dimethylamino)acrylamide as a versatile cyclohexyl-containing building block has been accomplished by microwave irradiation of a (**4**) 2-cyano-*N*-cyclohexyacetamide (**3**) with dimethylformamide-dimethylacetal (*DMF-DMA*) (**Scheme 1**). IR spectrum revealed to three absorption bands at 3342, 2186 and 1656 cm^{-1} due to NH, CN, C=O, respectively. Its ^1H NMR revealed signals at δ 3.09 and at δ 7.66 due to *N, N*-dimethyl amino and CH proton, respectively, in addition to an aliphatic multiplied in the region δ 1.4-1.7. Its mass spectrum revealed a peak at *m/z* 221 corresponding to its molecular ion



Scheme 1. *Synthesis of (E)-2-cyano-N-cyclohexyl-3-(dimethylamino)acrylamide (***4***)*

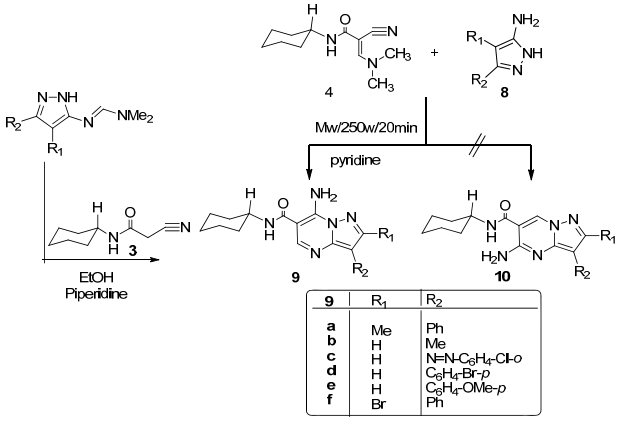
The reactivity of enaminonitrile **4** towards some nitrogen nucleophiles was investigated. Thus, treatment of compound **4** with hydrazine hydrate, phenylhydrazine derivatives in refluxing isopropyl alcohol furnished the novel pyrazoles **5a-c** as displayed in **scheme 2**. The IR spectra of compound **5a-c** were free of Nitrile function and showed the absorption band for NH and NH_2 in the region 3409-3336 cm^{-1}. The formation of compounds **5a-c** is assumed to take place *via* a *Michael-type* addition of the amino group of hydrazines to enaminone double bond in (*E*)-2-cyano-*N*-cyclohexyl-3-(dimethylamino) acrylamide monitored by loss dimethylamine (**scheme 2**). In the same manner, the enaminonitrile **4** reacts with guanidine in refluxing isopropyl alcohol to provide a high yield of a single product (as examined by TLC). That was identified as 2,4-diamino-*N*-cyclohexylpyrimidine-5-carboxamide (**7**) permitting to its elemental and spectral analysis (*c.f.* Experimental part).



Scheme 2. *Reaction of Enaminonitrile 4 with hydrazine hydrate derivatives and guanidine*

The reactivity of (*E*)-2-cyano-*N*-cyclohexyl-3-(dimethylamino) acrylamide (**4**) towards some heterocyclic amines was also investigated. Thus, when compound **4**

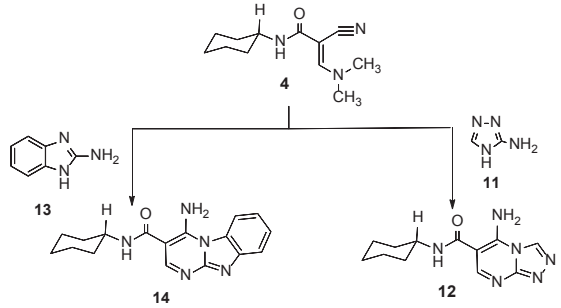
was treated with 5-amino pyrazole derivatives **8a-f** in pyridine it furnished in each example, a single products were identified as pyrazolo[1,5-*a*]pyrimidine derivatives **9a-f**, The structure **9a** was achieved by independent synthesis of compound **9**a *via* reaction of 5-*N*-(*N*,*N*-dimethylaminomethylene) imino3-phenyl-1*H*-pyrazole with 2-cyano-*N*-cyclohexy acetamide **3** in refluxing ethanol and the presence of catalytic amount of piperidine that afforded a product identical in all respects (mp.; TLC and spectra) with that achieved from of the Enaminonitrile **4** and 5-aminopyrazoles derivatives **8a-f** (**Scheme 3**)



Scheme 3. *Reaction of Enaminonitrile 4 with 5-amino pyrazole derivatives 8a-f*

In a similar manner, compound **4** reacted with 3-amino-1,2,4-triazole (**11**) to afford triazole [4,3-*a*] pyrimidine derivatives (scheme **4**).The mass spectrum of the isolated product revealed a peak at m/z 309 corresponding to its molecular ion. It's an IR spectrum reveled two characteristic bands in the region 3430-3274cm^{-1} due to NH and NH_2 and band at 1662 cm^{-1} due to the carbonyl group and no absorption band for Nitrile-function.

Finally, the Enaminonitrile **4** reacts with 2-aminobenzimidazole **(13)** to give 4-amino-*N*-cyclohexyl-4,6-dihydropyrimido[1,2-*b*] indazole-3-carboxamide **14** (Scheme **4**). The structure of the isolated product was confirmed on the basis of the elemental analysis and spectral data (*c.f.* Experimental part).



Scheme 4. *Reaction of* Enaminonitrile **4** *with 3-amino-1,2,4-triazole and 2-aminobenzimidazole*

Table. 1 *Optimized bond length Å, and bond and dihedral angle degrees of Compounds* **5a** *and* **9a** *via DFT B3LYP/6-31G(d)*

Compound **5a**				Compound **9a**			
Parameters of bond lengths	Å	Parameters of bond angles	Degrees	Parameters of bond lengths	Å	Parameters of bond angles	Degrees
C23-N27	1.3836	N27-C23-N30	122.8540	N28-N30	1.3699	C3-N17-C20	126.0873
C20-O21	1.2557	C23-N30-N31	113.8049	N30-C32	1.3620	N30-N28-C23	123.5823
N30-N31	1.3756	C24-N31-N30	106.9212	N17-C3	1.4709	N25-C23-N28	116.5805
C24-C22	1.5270	N18-C20-O21	120.6569	C20-O19	1.2771	C31-C24-N29	131.6775
C22-C23	1.5174	H29-N27-C23	116.4661	N29-C22	1.4947	N28-C24-N29	123.6158
N30-H26	1.0052	H19-N18-C20	113.7350	N29-C24	1.3177	N17-C20-C21	117.5352
N27-H28	1.0095	N18-C2-C3	111.6088	C24-N23	1.4136	C2-C3-N17	110.8324
N18-H19	1.0146	C1-C2-C3	111.4826	N28-C23	1.3902	C38-C39-C40	117.7719
N18-C20	1.0690	C1-C2-C6	111.4599	C23-C21	1.3872	C23-N25-H27	119.5643
N18-C3	1.4717	C3-C4-C5	111.6289	N28-N30	1.3699	O19-C20-C21	123.3318
C2-C3	1.5466	H29-N27-C23-N30	118.4812	C23-N25	1.3485	O19-C20-N17-H18	2.5675
C3-C4	1.5444	C22-C23-N30-N31	-1.7765	C31-C39	1.4615	N25-C23-C21-C20	-4.0106
N18-H19	1.0147	C22-C24-N31-N30	0.4818	C33-C32	1.4969	N30-N28-C24-N29	179.7452
C3-H17	1.0947	N18-C20-O21-C22	179.3091	C2-C3	1.5456	N28-C24-N29-C22	5.11674

Table 2 *Energetics of the ground state of* **5a** *and* **6a** *using DFT B3LYP/6-31G(d)*

Compound **5a**					Compound **6a**	
E_T (au)	-685.2566			E_T (au)	-685.20751	
E_{HOMO} (au)	-0.23880			E_{HOMO} (au)	-0.22029	
E_{LOMO} (au)	-0.18299			E_{LOMO} (au)	-0.15414	
Eg (eV)	1.51866			Eg (eV)	1.800034	
μ (D)	4.7898			μ (D)	6.8089	
Net charges		N27	-0.612	Net charges	N26	-0.764
		N30	-0.448		N30	-0.392
		N31	-0.147		N29	-0.253
		N18	-0.546		N18	-0.640
		O21	-.0436		O21	-0.477
		H19	0.302		H19	0.318
		C20	0.563		C20	0.561
		C3	-0.032		C3	0.044
		C24	0.002		C24	0.034

[a] Eg= E_{LOMO} - $E_{HOMO.}$

MOLECULAR ORBITAL CALCULATIONS

Geometrical optimization of compounds **5a** and **9a** proceeded at DFT/B3LYP hypothesis utilizing the Gaussian 09W program[38,39], which explain why (*E*)-2-cyano-*N*-cyclohexyl-3-(dimethylamino)acrylamide (**4**) reacted with hydrazine hydrate, as representative examples of nucleophilic reagent, to yield the corresponding novel pyrazoles **5a-c** with excellent yield rather than compound **6a-c**. On the other hand, the cyclization of acrylamide **4** with 5-amino pyrazole derivatives **8a-f** did not lead to the formation of a pure sample of the corresponding pyrazole[1,5-*a*] pyrimidine derivatives **9a-f**. Furthermore, DFT calculation was employed to study the stability of the pyrazole **5a** and pyrazolo[1,5-*a*] pyrimidine **9a** are both have 1*H*-pyrazole moiety, nevertheless they differ in the arrangement of the rings with pyrazole moiety with respect to the pyrazole **5a** or pyrazolo [1,5-*a*] pyrimidine **9a** rings. The optimized geometries (bond lengths and bond angles) as well as ground state energies total energy E_T, energy of highest occupied MO E_{HOMO}, energy of lowest unoccupied MO E_{LUMO}, energy gap E_g, dipole moment μ, and net charge on pyrazole **5a** and pyrazolo [1,5-*a*] pyrimidine **9a** rings using DFT/B3LYP/6-31G(d) are presented in Table **1,** Table **2** , Figure. **2** and Figure **3**

From the results of Table **1**, Table **2** and Figure. **2** and Figure **3**, the following conclusions were concluded:

(1)- The optimized bond length of both pyrazole 5a is fall in range 1.0052 to 1.5444 the same agreement with experimental[40] also pyrazolo [1,5-*a*] pyrimidine 9a falls in the range from 1.3177 to 1.5456 Å which are in good agreement with the experimental data 1.3601-1.7830 Å[41], for C=O bond of pyrazoles derivatives the optimized length obtained by B3LYP/6-31G(d) is 1.2557 Å were slightly longer than the experimental value 1.2307 Å[42] .

(2)- The bond angles for DFT/ B3LYP/6-31G (d) described in Table 1 For both pyrazole 5a and amino pyrazolo[1,5-*a*] pyrimidine 9a, the two compounds are nonplanar, where both the pyrazole are out of the molecular plane.

(4) For pyrazole 5a, the pyrazole are out of the molecular plane by -1.7765(C22-C23-N30-N31) and -0.4818(C22-C24-N31-N30); respectively, which permit the interaction with the appropriate hydrazine hydrate to afford the corresponding target molecule, compound 5a (85%).

(5) For amino pyrazolo [1,5-*a*] pyrimidine 9a, the pyrazol[1,5-*a*] pyrimidine was out of the molecular plane by -4.0106(N25-C23-C21-C20) and 5.1167 (N28-C24-N29-C22), respectively, which lead to stability between phenylpyrazolo[1,5-*a*]pyrimidine and cyclohexyl ring.

From the above results (**1**–**5**), it is clear that as the pyrazole **5a** and pyrazolo [1,5-*a*] pyrimidine **9a**, originated close to the molecular plane of the pyrazole moiety. On the other hand, as the two compounds, **5a** and **9a** moieties go far from the molecular plane of the pyrazole ring, by increasing its dihedral angles.

(6) The two *p*-isoelectronic structures **5a** and **6a** are different in order of stability, even though 1*H*-pyrazole **5a** seems a more stable than pyrazole **6a** by 0.2814 eV (≈27. 148 kcal).

(7) From the calculations of the energy gap, E_g, which measure the chemical activity, pyrazole **5a** was found to be more reactive than amino pyrazole **6a** by -685.257 kcal.

(8) The polarity or charge separation over the molecule, which is measured by the dipole moment μ, showed that μ of pyrazole **5a** < μ of pyrazole **6a** by 2.0191D as displayed in **Table 2**.

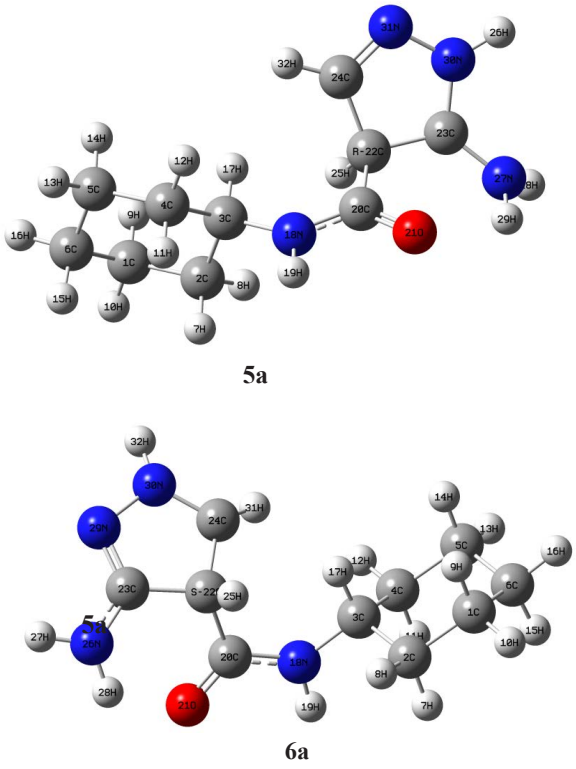


Figure.2 *Optimized geometry and numbering system, of* **5a** *and* **6a** *utilizing DFT B3LYP/6-31G(d)*

(9) The energies of the π-isoelectric compounds 7-amino-*N*-cyclohexyl-2-methyl-3-phenyl pyrazolo[1,5-*a*]pyrimidine-6-carboxamide **(9a)** and 5-amino-*N*-cyclohexyl-2-methyl-3-phenylpyrazolo[1,5-*a*]pyrimidine-6-carboxamide (**10a**) are different in order of stability as shown in **Table 3**, even though phenylpyrazolo[1,5-*a*]pyrimidine-6-carboxamide **9a** seems a more stable than phenylpyrazolo[1,5-*a*]pyrimidine-6-carboxamide **10a** by 0.4269 eV (≈41.1941 kcal).

(10)- Energy gap, E_g calculations measure the chemical activity, phenylpyrazolo[1,5-*a*] pyrimidine-6-carboxamide **9a** was found to be more reactive than amino phenylpyrazolo[1,5-*a*]pyrimidine-6-carboxamide **10a** by -1124.049 kcal.

(**11**) Dipole moment μ (Charge separation polarity) of pyrazolo[1,5-*a*]pyrimidine **9a** < μ of pyrazolo[1,5-*a*]pyrimidine **10a** by 2.8866D.

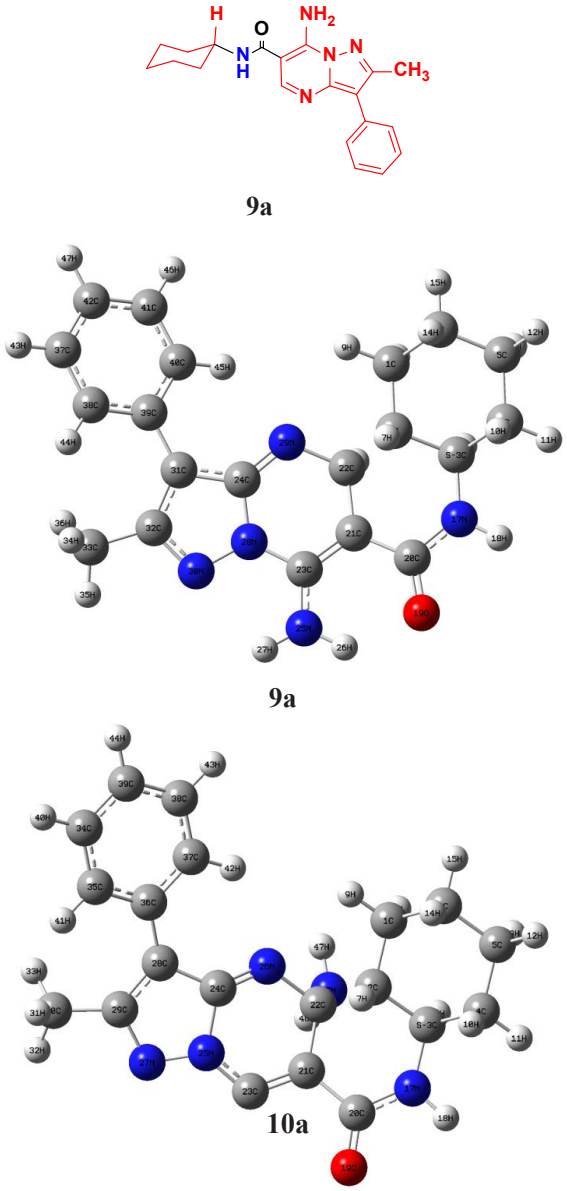


Figure.3 *Optimized geometry and numbering system of* **9a** *and* **10a** *using DFT B3LYP/6-31G(d)*

Table 3 *Energetics of the ground state of* **9a** *and* **10a** *using DFT B3LYP/6-31G (d)*

Compound **9a**				Compound **10a**	
E_T (au)	-1124.049		E_T (au)	-1123.2926	
E_{HOMO} (au)	-0.21096		E_{HOMO} (au)	-0.19870	
E_{LOMO} (au)	-0.18885		E_{LOMO} (au)	-0.16090	
Eg (eV)	0.601644		Eg (eV)	1.028591	
μ (D)	2.8866		μ (D)	8.1041	
Net charges		N30 -0.243	Net charges	N26	-0.345
		N28 -0.698		N25	-0.604
		N29 -0.368		N27	-0.168
		C20 0.486		C28	-0.062
		O19 -0.541		O19	-0.466
		N25 -0.775		N45	-0.598
		C23 0.607		C23	0.278
		C21 0.043		C21	-0.075
		C32 0.225		C29	0.206

[a] Eg= E_{LOMO} - $E_{HOMO.}$

From results (**6-11**) we established that Compounds amino-*N*-cyclohexyl-1*H*-pyrazole derivatives **5a** and **6a** are *the p*-isoelectronic molecule, as outlined in **Scheme 2**, compound **5** can be obtained using alternative pathway. DFT calculations at the same level of theory DFT B3LYP/6-31G(d) for both *p*-isoelectronic structures **5a** and **9a** were performed. The geometry and ground state energies of both structures are presented in Table **1,** Table **2** and Table **3** and Figure. **2** and Figure **3** the results of DFT calculations predicted that structure **5a** is more stable than structure **6a** by only ≈ 27.1 kcal. It is also establish that the structure **9a** is more chemically active than structures **10a** by only ≈ 41.1941 kcal. This implies that the two structures have almost the same order of stability, reactivity and both can chemically exist.

Vibrational assignment and ^{1}H NMR and ^{13}C NMR calculations of compound 9a

The optimized structure phenylpyrazole[1,5-*a*] pyrimidine-6-carboxamide **9a** is displayed in **Figure.2**, and selected bond lengths, bond angles, and

Table 4. *Comparison of the experimental and calculated vibrational frequencies and ^{1}H NMR and ^{13}C NMR calculations of* **9a.**

Compound 9a										
Vibrational frequencies			*^{1}H NMR and ^{13}C NMR calculations*							
PED (≥10%) Assignment	Scaled frequencies 6-31G(d)	Experimental FT-IR (cm-1)	Atom	Experimental (ppm) (DMSO)	Calculated (ppm) B3LYP 6-31G(d) (DMSO)	Calculated (ppm) HF 6-31G(d) (DMSO)	Atom	Experimental (ppm) (DMSO)	Calculated (ppm) B3LYP 6-31G(d) (DMSO)	Calculated (ppm) HF 6-31G(d) (DMSO)
ν (NH)	3463.23	3340. 22	H10	1.3121	0.7254	1.4409	C1	17.212	17.3982	34.9180
ν(NH2)	3252.23	3262.51	H12,13,15	1.4921	0.8285	1.5440	C4	22.932	23.0156	40.5352
ν (=CH-H)	3086.28	3073.21	H7	1.5230	0.9491	1.6646	C2	28.102	36.6616	54.1812
ν (=C-H)	3029.88	3011.10	H11	1.5520	1.0554	1.7709	C3	33.825	45.7590	63.2790
ν (C-H)	2893.23	2811.32	H35,36	2.7903	1.6269	2.3424	C22	47.134	56.5303	74.0494
ν (C=O)	1693.23	1648.25	H9	1.8233	1.6923	2.4078	C21	112.723	76.1330	93.6533
			H34	2.7901	1.9200	2.6355	C31	125.701	107.7100	125.2900
			H16	2.0234	2.1808	3.5263	C42	127.512	111.9560	129.4752
			H18	3.5301	3.3156	4.0311	C37	128.802	112.0402	129.5590
			H48	7.3212	4.0991	4.8146	C38	129.314	112.2100	129.7297
			H27	8.4202	4.2394	3.9541	C41	133.225	112.3809	129.9006
			H47	7.3514	6.5096	7.2251	C40	136.432	113.6583	131.1783
			H46	7.3403	6.5609	7.2764	C39	138.442	117.0133	134.5327
			H43	7.4481	6.6362	7.3517	C23	139.311	126.1023	143.6221
			H44	7.4820	6.8263	7.5418	C24	161.401	138.6373	156.1572
			H26	8.4201	7.2351	7.9506	C32	167.300	140.8723	158.3872
			H45	9.2111	7.7370	8.4526	C20	169.0231	153.1230	170.6722

dihedral angles are scheduled in **Table 1** designed by B3LYP/6-31G(d). IR frequencies of compound **9a** were calculated using the DFT/B3LYP methods with the 6-31G(d) basis set. The vibrational band assignments were made using the Gauss-View molecular visualization program. **Table 4** shows the observed and calculated IR spectra of this compound. Calculated vibrational frequencies of **9a** at DFT/B3LYP levels were scaled by 0.96 and 0.89; respectively[43]. The IR spectra have some characteristic bands of stretching vibrations of NH, NH_2, =CH-H, =C-H, C-H, and C=O. The structure that contains NH displays stretching vibrations of NH in the region 3300-3500 cm^{-1} [45]. The NH and NH_2 stretching mode observed at 3340.2, 3262 cm^{-1}experimentally; respectively, and calculated at 3463.23, 3252.23cm^{-1} for B3LYP. The aromatic structure displays the presence of =CH-H stretching vibrations in the region 3000-3100 cm^{-1} [44] was observed at 3073.21 cm^{-1} experimentally and calculated at 3086.28 cm^{-1} for B3LYP. Moreover, The C=O absorption band appears in 1648 cm^{-1} experimentally and 1693.23 cm^{-1} for B3LYP (**Table 4**). As can be seen from a correlation graph in **Figure. 2** experimental data are found to require a better correlation for B3LYP Moreover; the vibrational frequencies calculated by the B3LYP method are more compatible to experimental values. Furthermore ^1H and ^{13}C NMR chemical shift calculations using the density functional theory-gauge including/invariant atomic orbitals (DFT-GIAO) and (HF-GIAO) approximations at the B3LYP/6-31G (d) level of theory, which were comparable with the experimental ^1H and ^{13}C chemical shift values for **9a** as displayed in **Table 4** ,which showed the proton chemical shift values are considered to be 0.72540-7.73700 ppm using B3LYP/6-31G (d) and 1.4409-8.4526 ppm using HF/6-31G (d), while the experimental results are observed to be 1.312-9.211 ppm. The atoms were numbered as in Figure. **2**. The theoretical result is in agreement with the experimental data, except the NH_2 proton (H27 and H26). This proton performs at 8.420 ppm and is shifted towards higher magnetic field than the calculated one by B3LYP/6-31G (d) and HF/6-31G (d). The difference between the calculated and the experimental data for proton (H27 and H26) is 4.2394, 3.954 and 7.2351, 7.9506 ppm for B3LYP and HF; respectively. The continuum solvation models are important computational methods for theoretical studies such as conductor-like polarizable continuum model (CPCM) used for compute aqueous solvation free energies for a number of organic molecules [45a,b], but this model fails in reproducing the experimental results for the hydrogen-bonded protons and specific solute-solvent interactions which thoroughly expected to explain the NMR spectra of compound **9a**. The calculated ^{13}C NMR and the experimental outcome are scheduled in **Table 4**. As can be seen, the agreement with experimental data is good. The largest differentiation in ^{13}C chemical shifts observed for C(21), C(31), C(42), C(38), C(41), (C37) and C(32), using B3LYP/6-31G(d), while the largest differentiation observed for C (1), C(4), C(3), C(22), C(23) and C (24), using HF/6-31G(d) method. As can be seen from **Table 4**, the theoretical ^1H and ^{13}C chemical shift results for **9a** are generally closer to the experimental ^1H and ^{13}C shift data.

Frontier Molecular Orbitals of compound 9a:

FMO (Frontier molecular orbital) is a powerful guiding approach in the electrical and optical properties, in addition to UV-Vis spectra and chemical reactions. The highest occupied molecular orbital (HOMO) acts as an electron donor and the lowest unoccupied molecular orbital (LUMO) acts as the electron acceptor. The energy gap between HOMOs and LUMOs connected to the biological activity of the molecule. 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. **Figure. 4** indications the distributions and energy levels of the HOMO, LUMO, and orbitals computed at the TD-DFT B3LYP/6-31G (d) level for **9a**. The positive and negative phases are represented in red and green colors, respectively. As appreciated from **Figure. 4,** Though DFT calculates the ground states energetics for various materials, it be unsuccessful in predicting the energy gaps between occupied and unoccupied states which is less than the half of the observed value. Consequently, in order to overcome this problem hybrid functional was used. General, hybrid functional were used to improve the description of the ground state energies for small molecules[46-47]. One of the most commonly hybrid functional used is B3LYP which leads to improved band gaps as good as that obtained from sophisticated correlated calculation[48] so to rationalized this increased accuracy by comparison with results from time-dependent DFT (TD-DFT) calculations so we found the HOMO–LUMO gap energy (2.2474 eV). This energy gap of the excited state gives the compound **9a** more stable[49, 50] as displayed in Figure **4**.

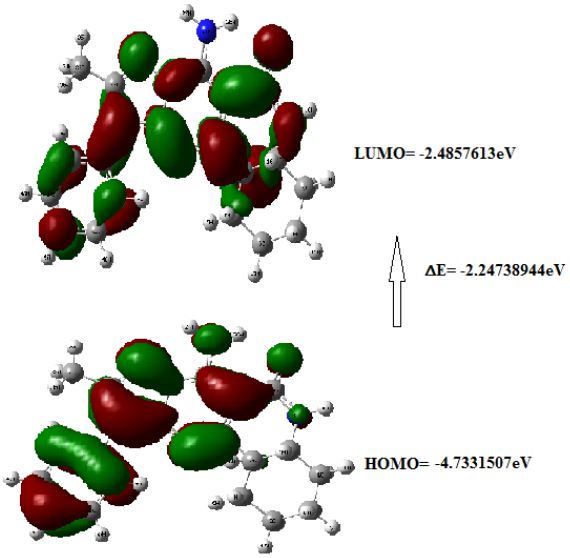


Figure 4. *Gap energy (HOMO–LUMO) (eV) are calculated for* **9a** *using TD-DFT B3LYP/6-31G (d)*

CONCLUSION

Our investigation we synthesized a variability of fused heterocyclic systems consolidating cyclohexyl moiety *via* the reaction of (*E*)-2-cyano-*N*-cyclohexyl-3-(dimethylamino)acrylamide (**4**) with appropriate 1,3-binucleophiles exhausting conventional procedures other than microwave irradiation. Furthermore, a theoretical interpretation of the regioselectivity of the cyclocondensation reactions was carried out exhausting DFT concentrated with DFT/B3LYP and HF methods with the 6-31G (d) basis set combination. Comprehensive theoretical and experimental structural studies pyrazolo[1,5-*a*] pyrimidine **9a** have been carried out by elemental analysis, FTIR, ^{1}H NMR, and Mass. Optimized molecular structure and harmonic vibrational frequencies have been investigated by DFT/B3LYP 6-31G(d) basis set.

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