Heterocyclic Letters
Vol. 13| No.3|525-531|May-July|2023
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS OF DERIVATIVES OF 1-(3-(3-(1H-1,2,3-TRIAZOLE-1-YL) PHENYL)-4,5-DIHYDRO-1H-PYRAZOL-1-YL) ETHANONE FROM 3-AMINO ACETOPHENONE

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ABSTRACT:
In the present study, we tend to synthesize new organic compounds. Different Substituted 1,2,3-triazole were synthesized by the cyclization of 1-(3-azidophenyl) ethanone; which was obtained by coupling of diazotization of 3-amino acetophenone[i] with sodium azide; with different active methylene compounds such as malononitrile, methyl cyanoacetate, ethyl acetoacetate, diethyl malonate severally. The structures of the ready compounds were characterized by ^{1}H NMR, mass and elemental analysis.

KEYWORDS: 3-Amino acetophenone, p-chloro benzaldehyde, Malononitrile, methyl cyanoacetate, ethyl acetoacetate, diethyl malonate, acetic acid, propionic acid.

INTRODUCTION:

For the total asymmetric synthesis of pactamycin 3-Aminoacetophenone was used as one of the raw materials[i]. Curcumin mimics with substituted sulfonyl group were also synthesized by 3-amino acetophenone. In addition to being used in the synthesis of selective antagonists at human A2B adenosine receptors, 3-Aminoacetophenone has potential antibacterial properties[ii]. It is also used in the synthesis of HIV-1 integrase inhibitors. 3'-Aminoacetophenone acts as a bifunctional coupling agent during the synthesis of pyrimidines[iii]. The development of nitrogen-containing heterocyclic compounds has received considerable attention in both medicinal and industrial chemistry. 1,2,3-Triazole derivatives[iv-vi], which are a remarkable class of heterocycles due to their wide range of applications as drugs due to their wide range of biological activities such as antimicrobial, anticancer, anticonvulsant and analgesic activity. Considering these findings, we focused on the synthesis of simpler substances[viii-x].

EXPERIMENTAL SECTION:

Melting points were taken on a SESW melting point apparatus and are uncorrected. 1H NMR spectra were recorded on a Varian-Mercury 200MHz spectrometer. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 instrument (70eV EI mode). Elemental analysis was

performed on a Yanaco CHN Corder MT-3 analyzer. All the chemicals and solvents were purchased from Loba Chemie (India), Merck (India), Spectrochem (India), and SRL (India).

Synthesis of 1-(3-azidophenyl) ethan-1-one 2:
1-(3-azidophenyl) ethyl-1-one **2** was prepared by a diazotization reaction of 3-amino acetophenone **1** followed by the reaction with sodium azide. In a round bottom flask, charged 6M aqueous solution of hydrochloric acid (20 ml) and 3-Amino acetophenone (5gms, 0.037 moles) at room temperature. Then cool reaction mass to 0°C. An aqueous solution of $NaNO_2$ (2.55gms, 0.037 moles in 5ml of H_2O) was added to the reaction mixture below 5°C. After completed addition of $NaNO_2$ solution, stirred reaction mass at same temperature for 10 minutes. Then, an aqueous solution of NaN_3 (2.4gms, 0.037 moles in 5ml of H_2O) was added dropwise to the reaction mixture below 5°C. After completed addition, stirred the reaction mixture at the ambient temperature for 2 hours. Progress of the reaction was monitored on TLC. (Mobile phase- Hexane: Ethyl acetate (7:3)). After completion of reaction on TLC, reaction mass extracted with 250ml of dichloromethane. Distilled out dichloromethane under vacuum to get product.

1-(3-azidophenyl) ethan-1-one 2:
Dark brown color oil. Yield 94.5%. MP 44°C-46°C. ^{1}H NMR (400MHz, $CDCl_3$): 8.16 (t, 1H), 7.92 (dd, 2H), 7.51 (d, 1H), 2.54 (s, 3H). Anal. Data for $C_8H_7ON_3$ (161.06): Calcd C 59.62, H 4.38, N 26.07. Found C 59.60, H 4.32, N 25.98.

Synthesis of 1-(3-azidophenyl)-3-(4-chlorophenyl) prop-2-en-1-one 3:
A mixture of the p-chloro benzaldehyde (0.012 moles) and 1-(3-azidophenyl) ethan-1-one **2** 0.01 moles) dissolved in ethanol (20 mL) was added slowly to an aqueous solution of potassium hydroxide (0.0128 moles) in water (3 mL). The reaction mixture was stirred in the crushed-ice bath for 2 h and stirred at 20–25°C for 4 h. The mixture was filtered and the solid was washed with cold water and cold ethanol. The product was crystallized from ethanol to give 1-(3-azidophenyl)-3-(4-chlorophenyl) prop-2-en-1-one **3.**

1-(3-azidophenyl)-3-(4-chlorophenyl) prop-2-en-1-one 3:
Buff color oil. Yield 86%. MP 107°C-109°C. ^{1}H NMR (400MHz, $CDCl_3$): 8.32-8.19 (m,2H), 7.98-7.91 (m,1H), 7.75 (dd, 1H), 7.64-7.48 (m, 4H), 7.44 (d, 2H). Anal. Data for $C_{15}H_{10}ClN_3O$ (283.051): Calcd C 63.50, H 3.55, Cl 12.49, N 14.81, Found C 63.44, H 3.52, Cl 12.39, N 14.78.

General method for the synthesis of 5-amino-1-(3-(3-(4-chlorophenyl) acryloyl) phenyl-1H-1,2,3-triazole-4-carbonitrile 4a-d:
Compound **4a-d** were prepared by the reaction of 1-(3-azidophenyl)-3-(4-chlorophenyl) prop-2-en-1-one **3** with active methylene compound (Malononitrile, methyl cyano acetate, ethyl aceto acetate, dimethyl malonate). A cold solution of sodium methoxide (0.00088 mole, in 20 mL absolute methanol) was added to the mixture of active methylene compounds (0.00064 mole) and 1-(3-azidophenyl)-3-(4-chlorophenyl) prop-2-en-1-one **3** (0.00058 mole) and stirred for 1 h at 0°–5°C. Then the mixture was heated under reflux on an oil-bath for 4 h. Finally, the mixture was acidified with concentrated hydrochloric acid. Compound 3a-f was separated and crystallized from methanol.

5-amino-1-(3-(3-(4-chlorophenyl) acryloyl) phenyl-1H-1,2,3-triazole-4-carbonitrile 4a:
Yellow color solid. Yield 49%. MP 122°C-124°C. ^{1}H NMR (400MHz, $CDCl_3$): 10.81 (s, 2H),

8.19 (d, 1H), 8.07 (d,1H), 7.71-7.55 (m, 2H), 7.53-7.37 (m, 6H). Anal. Data for $C_{18}H_{12}ClN_5O$ (349.07): Calcd C 61.81, H 3.46, Cl 10.13, N 20.02, Found C 61.77, H 3.26, Cl 10.03, N 19.99.

Methyl-5-amino-1-(3-(3-(4-chlorophenyl) acryloyl) phenyl-1H-1,2,3-triazole-4-carboxylate 4b:
Brown color solid. Yield 55%. MP 132°C-134°C. ^{1}H NMR (400MHz, $CDCl_3$): 10.88 (s, 2H), 8.19 (t, 1H), 8.09 (d,1H), 7.66 (d,1H), 7.54-7.33 (m, 7H), 3.95(s, 3H). Anal. Data for $C_{19}H_{15}ClN_4O_3$ (382.08): Calcd C 59.62, H 3.95, Cl 9.26, N 14.64, Found C 59.55, H 3.90, Cl 9.20, N 14.55.

Ethyl-5-methyl-1-(3-(3-(4-chlorophenyl) acryloyl) phenyl-1H-1,2,3-triazole-4-carboxylate 4c:
Buff color solid. Yield 36%. MP 145°C-147°C. ^{1}H NMR (400MHz, $CDCl_3$): 8.2 (t,1H), 8.10 (d,1H), 7.67 (d, 1H), 7.54-7.38 (m, 7H), 4.33 (q, 2H), 2.58 (s, 3H), 1.39 (t, 3H). Anal. Data for $C_{21}H_{18}ClN_3O_3$ (395.10): Calcd C 63.72, H 4.58, Cl 8.96, N 10.62, Found C 63.72, H 4.44, Cl 8.75, N 10.60.

Ethyl-1-(3-(3-(4-Chlorophenyl) acryloyl) phenyl)-5-oxo-4,5-dihydro-1H-1,2,3-triazole-4-carboxylate 4d:
Yellow color solid. Yield 37%. MP 141°C-143°C. ^{1}H NMR (400MHz, $CDCl_3$): 8.07 (d,1H), 7.96 (t, 1H), 7.89 (d, 1H), 7.60-7.40 (m, 7H), 5.35 (s, 1H), 4.19 (q, 2H), 1.40 (t, 3H). Anal. Data for $C_{21}H_{18}ClN_3O_3$ (395.10): Calcd C 63.72, H 4.58, Cl 8.96, N 10.62, Found C 63.72, H 4.44, Cl 8.75, N 10.60.

General method for the synthesis of Compound 5a-d and Compound 6a-d:
Compounds **5a-d** and Compounds **6a-d** were prepared by the reaction of compounds **4a-d** with hydrazine hydrate and acetic acid or propionic acid. A mixture of compound **4a-d** (0.01 mol), hydrazine hydrate (0.03 mol), acetic acid or propionic acid (50 mL) was refluxed for 3 h, then poured into crushed-ice. The precipitate was separated by filtration, washed with water and the crude products were obtained, which were crystallized from ethanol.

1-(3-(1-acetyl-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl) phenyl)-5-amino-1H-1,2,3-triazole-4-carbonitrile 5a:
Yellow color solid. Yield 52%. MP 178°C-180°C. ^{1}H NMR (400MHz, $CDCl_3$): 10.47 (s, 2H), 7.68 (d, 1H), 7.54 (t,1H), 7.41 (dd, 2H), 7.31 (d, 2H), 7.21 (d, 2H), 5.74 (t, 1H), 3.12 (dd, 1H), 2.92-2.84 (m, 1H), 2.05 (s,3H). Anal. Data for $C_{20}H_{16}ClN_7O$ (405.11): Calcd C 59.19, H 3.97, Cl 8.73, N 24.16, Found C 59.10, H 3.89, Cl 8.55, N 24.10.

Methyl-1-(3-(1-acetyl-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl) phenyl)-5-amino-1H-1,2,3-triazole-4-carboxylate 5b:
Yellow color solid. Yield 44%. MP 185°C-187°C. ^{1}H NMR (400MHz, $CDCl_3$): 10.84 (s, 2H), 7.60 – 7.52 (m, 2H), 7.39 (t, 1H), 7.30 (dd, 3H), 7.17 (d, 2H), 5.61 (t, 1H), 3.95 (s, 3H), 3.07 (d, 1H), 2.91 (d, 1H), 1.96 (s, 3H). Anal. Data for $C_{21}H_{19}ClN_6O_3$ (438.12): Calcd C 57.47, H 4.36, Cl 8.08, N 19.15, Found C 57.33, H 4.34, Cl 8.00, N 18.99.

Ethyl-1-(3-(1-acetyl-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl) phenyl)-5-methyl-1H-1,2,3-triazole-4-carboxylate 5c:
Buff color solid. Yield 38%. MP 164°C-166°C. ^{1}H NMR (400MHz, $CDCl_3$): 7.54 (dd, 2H), 7.38 (dd, 2H), 7.28 (d, 2H), 7.17 (d, 2H), 5.61 (s, 1H), 4.37 – 4.29 (m, 2H), 3.07 (d, 1H), 2.91

(d, 1H), 2.34 (s, 3H), 1.96 (s, 3H), 1.37 (t, 3H). Anal. Data for $C_{23}H_{22}ClN_5O_3$ (451.14): Calcd C 61.13, H 4.91, Cl 7.84, N 15.50, Found C 61.10, H 4.88, Cl 7.82, N 15.44.

Ethyl-1-(3-(1-acetyl-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl) phenyl)-5-oxo-4,5-dihydro-1H-1,2,3-triazole-4-carboxylate 5d:
Yellow color solid. Yield 69%. MP 141°C-144°C. ^{1}H NMR (400MHz, $CDCl_3$): 8.37 (d, 1H), 7.54 (t, 1H), 7.43 – 7.29 (m, 3H), 7.23 (d, 2H), 6.86 (t, 1H), 5.56 (t, 1H), 5.23 (s, 1H), 4.16 (q, 2H), 3.08 (dd, 1H), 2.88 (dd, 1H), 1.89 (s, 3H), 1.37 (t, 3H). Anal. Data for $C_{22}H_{20}ClN_5O_4$ (453.12): Calcd C 58.22, H 4.44, Cl 7.81, N 15.43, Found C 58.12, H 4.34, Cl 7.77, N 15.22.

5-amino-1-(3-(5-(4-chlorophenyl)-1-propionyl-4,5-dihydro-1H-pyrazol-3-yl) phenyl)-1H-1,2,3-triazole-4-carbonitrile 6a:
Brown color solid. Yield 67%. MP 174°C-176°C. ^{1}H NMR (400MHz, $CDCl_3$): 10.47 (s, 2H), 7.68 (d, 1H), 7.54 (t, 1H), 7.48 – 7.35 (m, 2H), 7.31 (d, 2H), 7.21 (d, 2H), 5.79 (t, 1H), 3.12 (dd, 1H), 2.87 (dd, 1H), 2.51 (q, 2H), 1.23 (t, 3H). Anal. Data for $C_{21}H_{18}ClN_7O$ (419.13): Calcd C 60.07, H 4.32, Cl 8.44, N 23.35, Found C 60.00, H 4.22, Cl 8.39, N 23.31.

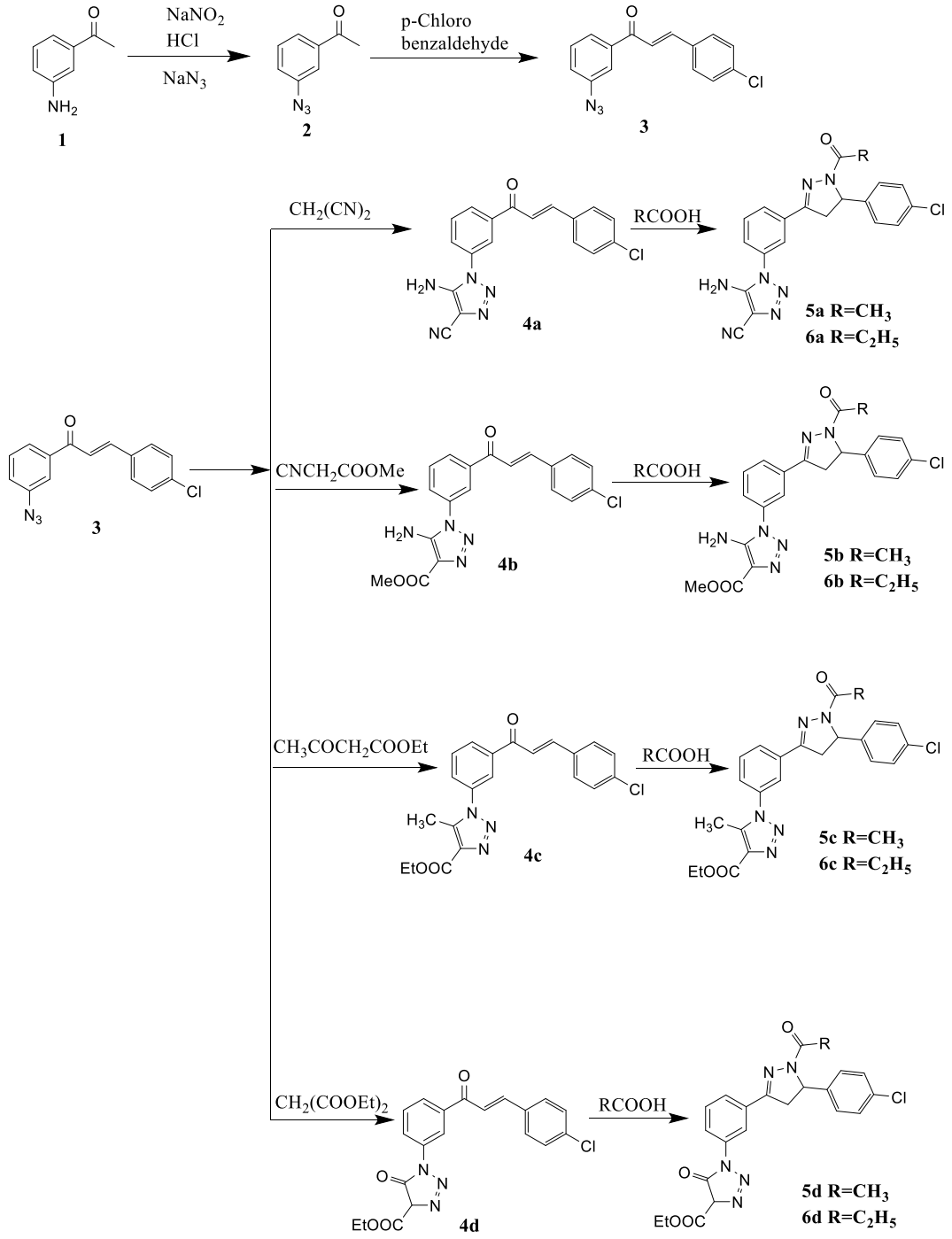
Methyl-5-amino-1-(3-(5-(4-chlorophenyl)-1-propionyl-4,5-dihydro-1H-pyrazol-3-yl) phenyl)-1H-1,2,3-triazole-4-carboxylate 6b:
Buff color solid. Yield 77%. MP 180°C-182°C. ^{1}H NMR (400MHz, $CDCl_3$): 10.32 (s, 2H), 7.73 (d, 1H), 7.56 (t, 1H), 7.45 – 7.26 (m, 4H), 7.21 (d, 2H), 5.79 (t, 1H), 3.95 (s, 3H), 3.12 (dd, 1H), 2.87 (dd, 1H), 2.51 (q, 2H), 1.22 (t, 3H). Anal. Data for $C_{22}H_{21}ClN_6O_3$ (452.13): Calcd C 58.34, H 4.67, Cl 7.83, N 18.56, Found C 58.22, H 4.55, Cl 8.44, N 18.40.

Ethyl-1-(3-(5-(4-chlorophenyl)-1-propionyl-4,5-dihydro-1H-pyrazol-3-yl) phenyl)-5-methyl-1H-1,2,3-triazole-4-carboxylate 6c:
Buff color solid. Yield 52%. MP 160°C-162°C. ^{1}H NMR (400MHz, $CDCl_3$): 7.53 (t, 2H), 7.39 (dd, 2H), 7.28 (d, 2H), 7.18 (d, 2H), 5.65 (t, 1H), 4.32 (q, 2H), 3.12 – 3.04 (m, 1H), 2.94 – 2.86 (m, 1H), 2.56 (q, 2H), 2.34 (s, 3H), 1.38 (t, 3H), 1.13 (t, 3H). Anal. Data for $C_{24}H_{24}ClN_5O_3$ (465.16): Calcd C 61.87, H 5.19, Cl 7.61, N 15.03, Found C 61.77, H 5.10, Cl 7.52, N 14.99.

Ethyl-1-(3-(5-(4-chlorophenyl)-1-propionyl-4,5-dihydro-1H-pyrazol-3-yl) phenyl)-5-oxo-4,5-dihydro-1H-1,2,3-triazole-4-carboxylate 6d:
Brown color solid. Yield 30%. MP 132°C-134°C. ^{1}H NMR (400MHz, $CDCl_3$): 8.32 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.37 (dd, J = 26.7, 7.6 Hz, 3H), 7.22 (d, J = 7.6 Hz, 2H), 6.87 (t, J = 1.4 Hz, 1H), 5.70 (t, J = 8.8 Hz, 1H), 5.44 (s, 1H), 4.15 (q, J = 6.0 Hz, 2H), 3.07 (d, J = 8.7 Hz, 1H), 2.93 (d, J = 8.7 Hz, 1H), 2.29 (q, J = 6.8 Hz, 2H), 1.35 (t, J = 6.0 Hz, 3H), 1.21 (t, J = 6.8 Hz, 3H). Anal. Data for $C_{23}H_{22}ClN_5O_4$ (467.14): Calcd C 59.04, H 4.74, Cl 7.58, N 14.97, Found C 58.99, H 4.91, Cl 7.44, N 14.89.

RESULT AND DISCUSSION:

Compound 3-Azido acetophenone **2** was prepared by a diazotization reaction of 3-amino acetophenone **1** followed by a reaction with sodium azide. Compound **3** was prepared by the reaction of compound **2** with 4-chloro benzaldehyde, which was further treated with active methylene compounds such as malononitrile, methyl cyanoacetate, ethyl acetoacetate and diethyl malonate to give compounds **4a-d**. Compounds **5a-d** and **6a-d** were prepared by reaction with hydrazine hydrate, acetic acid, and propionic acid, respectively. All the structures of synthesized compounds were assigned by spectral analysis.



CONCLUSION:

In this literature we have described synthetic methods of derivatives of 1-(3-(3-(1H-1,2,3-triazole-1-yl) phenyl)-4,5-dihydro-1H-pyrazol-1-yl) ethanone from 3-amino acetophenone. All the synthesized compounds were characterised and confirmed by spectral and analytical methods. The importance of such work lies in the possibility that the synthesized compounds might be more efficacious against bacterial and fungal species which could be helpful in designing potent antibacterial and antifungal compounds for therapeutic use hence recommend

future research.

ACKNOWLEDGEMENT:

The author Mohan Sagare is thankful to the Department of Chemistry, Institute of Science, Homi Bhabha State University, Mumbai-32. Also thankful to Dr. Bhushan Dabholkar, director of Sagchem LLP for his help and support.

REFERENCES:

i Heng S. D., Yan-F.W., Guo-L. S., Bin Q., Wang-J. D.; Synthesis of Some New 1-Acyl-5-aryl-3-(5-methyl-1-p-tolyl-1H-1,2,3-triazol-4-yl)-4,5-dihydro-1H-pyrazole; J. Heterocyclic Chem. 2012, **49**, 149-153.

ii Ratnamala Sonawane, Mohan Sagare; Synthesis of (3-(5-methyl-1-phenyl)-1H-1,2,3-triazol-4-yl)-4,5-dihydro-1H-pyrazol-1-yl) phenyl methanone and its derivatives from substituted anilines; Heterocyclic letter 2022, **12**, 753-758.

iii Bloom B.R.; Murray C.J.; Tuberculosis: Commentary on a Reemergent Killer; Science 1992, **257**, 1055.

iv Barnes P.F.; Bloch A.B.; Davidson P.T.; Snider D.E., Current Concepts: Tuberculosis in Patients with Human Immunodeficiency Virus Infection; N. Eng. J. Med. 1991, **324**, 1644.

v (a)I. V. Mashevskaya, S. V. Kol'tsova, E. V. Voronina, T. F. Odegova & A. N. Maslivets; Synthesis and Antimicrobial Activity of the Products of Interaction of 3-Aroyl-2,4-dihydro-1h-pyrrolobenzoxazine-1,2,4-triones with Urea and Thiourea; J. Pharm. Chem. 2001, **35**, 18; (b) Soliman, R.; Habib, N.S.; Ashour, F.A.; El-Taiebi; Synthesis and antimicrobial activity of novel pyrazole, pyrazoline, pyrazolinone and pyrazolidinedione derivatives of benzimidazole; M. Boll. Chim. Farm. 2001, **140**, 140.

vi Ahn, J.H.; Kim, H.-M.; Jung, S.H.; Kang, S.K.; Kim, K.R.; Rhee, S.D.; Yang, S.-D.; Cheon, H.G.; Kim, S.S.; Synthesis and DP-IV inhibition of cyano-pyrazoline derivatives as potent anti-diabetic agents; Bioorg. Med. Chem. Lett 2004, **14**, 4461.

vii (a) Nasr, Magda.N.A.; Said, S.A.; Novel 3,3a,4,5,6,7-Hexahydroindazole Arylthiazolylpyrazoline derivatives as Anti-inflammatory Agents; Arch. Pharm. (Weinheim) 2003, **336**, 551; (b) Tewari, A.K.; Mishra, A.; Synthesis and anti-inflammatory activities of N4, N5-disubstituted-3-methyl-1H-pyrazolo[3,4-c] pyridazines; Bioorg Med Chem. 2001, **9**, 715.

viii Kucukguzel, S.G.; Rollas, S.; Synthesis, characterization of novel coupling products and 4-arylhydrazono-2-pyrazoline-5-ones as potential antimycobacterial agents; Farmaco 2002, **57**, 583.

ix Kucukguzel, S.G.; Rollas, S.; Erdeniz, H.; Kiraz, M.; Ekinci, A.C.; Vidin, A.; Synthesis, characterization and pharmacological properties of some 4-arylhydrazono-2-pyrazoline-5-one derivatives obtained from heterocyclic amines; Eur. J. Med. Chem. 2000, **35**, 761.

x Nauduri, D.; Reddy, G.B.; Antibacetrials and Antimycotics: Part 1: Synthesis and Activity of 2-Pyrazoline Derivatives; Chem. Pharm Bull (Tokyo); 1998, **46**, 1254.

xi Santilli, A.A.; Kim, D.H.; Gregory, F.J.; Antitubercular Activity of Substituted 5-0xo-l-thiocarbamoyl-3-pyrazoline-4-alkanoic Acid Derivatives; J. Pharm. Sci. 1975, **64**, 1057.

xii Shaharyar, M.; Siddiqui, A.A.; Ali, M.A.; Sriram, D.; Yogeeswari, P.; Synthesis and in vitro antimycobacterial activity of N1-nicotinoyl-3-(4′-hydroxy-3′-methyl phenyl)-[(sub)phenyl]-2-pyrazolines; Bioorg. Med. Chem. Lett. 2006, **16**, 3947.

xiii El-Rayyes, N.R.; Hovakemian, G.H.; Hmoud, H. S.; Heterocycles. 3. Synthesis and spectral data of some 2-pyrazolines; J. Chem. Eng. Data 1984, **29**, 225.

xiv Oluwadiya J. O.; Some new phenolic pyrazoles from 2′-Hydroxychalcones; J Heterocycle

Chem. 1981, **18**, 1293.

xv Wiley, R.H.; Jarboe, C.H.; Hayes, F.N.; Hansbury, E.; Nielsen, J.T.; Callahan, P.X.; Sellars, M. C.; 1,3,5-Triaryl-2-pyrazolines for Use as Scintillation Solutes; J. Org. Chem. 1958, **23**, 732.

xvi Dong, H.-S.; Wei, K.; Wang, Q.-L.; Quan, B.; Zhang, Z.-Y.; Synthesis of 3-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-6-substituted-s-triazolo[3,4-b]-1,3,4-thiadiazoles; J Chin. Chem. Soc. (Taipei) 2000, **47**, 343.

xvii Dong, H.-S.; Wang, H.-C.; Gao, Z.-L.; Li, R.-S.; Cui, F.-H.; Tandem Michael addition/imino-nitrile cyclization synthesis of 2-amino-6-(1-aryl-5-methyl-1H-1,2,3-triazol-4yl)-4-phenylpyridine-3-carbonitrile; J. Heterocycle Chem. 2010, **47**, 389.

Received on February 17, 2023.