Synthesis, Antibacterial Activity and DFT Calculation of Naphtopyrano, Furo and Pyrazolo [3,2,e] [1,2,4]Triazolo-[1,5-c]Pyrimidine Derivatives

Dhiab Jabli¹ · Rim Milad² · Manef Abderrabba² · Mohamed Lotfi Efrif¹

Received: 5 February 2019 / Accepted: 1 July 2019 / Published online: 8 August 2019
 © The Author(s) 2019

Abstract

A new series of 3*N*-substituted triazolo-[1,5-*c*]pyrimidine **7**, **8** and **9** have been synthesized in good yields (78–91%) through a facile method using substituted 2-amino-3-cyano-pyrans **1**, 2-amino-3-cyano-4-methylfuran **2**, 1-Phenyl-3-thiomethyl-5-aminopyrazole-4-carbonitrile **3** as building block and cyanoacetic acid hydrazide as reagent in one framework. The structure of the synthesized compounds was established on the basis of their mass, spectral data and *DFT* at *B3LYP*.

Graphic Abstract

Keywords Naphthopyranotriazolopyrimidines phosphonates · Aminopyrazole · α -Functionalized iminoethers and pyrimidine

1 Introduction

Pyrano, furano and pyrazolopyrimidine are privileged structures, which attracted considerable attention in the designing of biologically active molecules. Pyranotriazolopyrimidine derivatives have attracted a great deal of interest due to their biological activities and their potential applications as pharmacological agents. Several derivatives of the pyranotriazolopyrimidine exhibit platelet anti-aggregating activity and local “inhibition of influenza, virus sialidase and mutagenic

activity [1], anti-genotoxic activity [2], antimicrobial activity [3], AChE or acetylhydrolase inhibition [4], and antifungal [5, 6]”. Moreover pyranotriazolopyrimidine derivatives are well known antigenotoxic, [7] and in the agrochemical field, showing herbicidal activity [8]. Among these heterocyclic, the furo-pyrimidine derivatives are an important class of heterocyclic compounds in pharmaceutical discovery research such that antiproliferative activity [9], antibacterial [5], anti-inflammatory [10], and herbicidal activities [11]. Recently, some furo-pyrimidines were shown to be potent VEGFR2 and EGFR [12]. Furthermore, 1,2,4-triazolopyrimidines derivatives has received considerable attention among synthetic chemists because molecules bearing this structural feature have been found to display a wide range of potent biological activities in medicinal chemistry, as antibacterial, antifungal, [13, 14] antiplatelet, antithrombotic, [15] anti-inflammatory and analgesic agents, [16] and in the agrochemical field, showing herbicidal activity [8]. According to these encouraging results and as a continuation of our

✉ Dhiab Jabli
 jabli.dhiab@gmail.com

¹ Laboratory of Selective Organic and Heterocyclic Synthesis-Biological Activity Evaluation, Department of Chemistry, Faculty of Sciences, El Manar University, El Manar II, 1060 Tunis, Tunisia

² Laboratoire Matériaux, Molécules et applications, Institut Préparatoire aux Etudes Scientifiques et Techniques, BP, La Marsa, Tunisia

Scheme 1 General reactions

interest works on heterocyclic compounds related to (pyrano, furano and pyrrolo)pyrimidines [17, 18], we wish to report herein the synthesis of new pyranotriazolopyrimidine **7**, furanotriazolopyrimidine **8** and pyrazolotriazolopyrimidine **9** in the hope of obtaining compounds of diverse biological activities. Hence a facile method has been attempted by incorporating triazole and pyrimidine rings with substituted 2-amino-3-cyano-pyrans **1**, 2-amino-3-cyano-4-methylfuran **2**, 1-Phenyl-3-thiomethyl-5-aminopyrazole-4-carbonitrile **3**, as building block in one framework (Scheme 1). Also, the compounds were investigated theoretically by density functional theory DFT and time-dependant density functional theory TD-DFT. (TDDFT) extends the basic thoughts of ground-state density-functional theory (DFT) to the treatment of excitations or more general time-dependent phenomena [19, 20].

2 Experimental Methods

2.1 General

Solvents and reagents were obtained from commercial sources and were dried and purified when necessary by standard techniques. Melting points were taken with a Kofler hot staged apparatus and are uncorrected. All reactions were monitored by thin layer chromatography (TLC) using precoated aluminium sheet silica gel Merck 60 F 254 and was visualized by UV lamp. IR spectra were carried out in the liquid state dissolved in chloroform with Perkin Elmer Paragon 1000 PC spectrometer or in solid state dispersion in KBr with a Perkin Elmer 1600 series FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian-Unity spectrometer at 300 MHz (300 MHz and 75 MHz, respectively) using TMS as an internal standard. Chemical shifts of protons were reported in parts per million (ppm) downfield from TMS. Coupling constants are reported in Hertz (Hz).

Elemental analyses were determined using an elemental vario EI III Elemental Analyser.

2.1.1 Synthesis of Cyanoacetic Acid Hydrazide

Cyanoacetic acid hydrazide was obtained according to the published method in literature [26] by careful addition of 9.91 g (0.10 mol) of ethyl cyanoacetate to hydrazine hydrate (5.00 g, 0.10 mol) with stirring at room temperature. The formed cyanoacetic acid hydrazide was filtered, washed with Et₂O, and dried (Mp: 108–110 °C. Yield: 90%).

2.1.2 Synthesis of 2-Amino-4-Aryl-3-Cyano-4H-Naphto-[2,1-b]-Pyrans **1**

The required naphto[2,1-b]pyrans **1** were obtained using known experimental procedures developed previously by Messaâd et al. [21, 22]. Following this typical experiment, a mixture of 2-naphtol (0.01 mmol, 1.5 g) and arylalkylidenmalononitrile (0.01 mmol, 1.7 g) in ethanol (30 mL) was refluxed for 10 h with the presence of (0.2 equivalent) of piperidine. The solvent was evaporated to dryness under reduced pressure. The solid was collected by filtration and purified by recrystallization from toluene (Scheme 2).

2.1.2.1 2-Amino-3-Cyano-4-(*p*-Chlorophenyl)-4H-Naphto-[2,1-b]-Pyran **1a** [21, 22] Yield: 68%; Mp: 231 °C. IR (ν_{max} , cm^{-1}): 3412, 3331, 2178 cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6 + CDCl_3) δ : 7.11–7.95 (m, 10H), 6.87 (br, s, 2H), 5.09 (s, 1H).

2.1.2.2 2-Amino-3-Cyano-4-(3,4-Dichlorophenyl)-4H-Naphto-[2,1-b]-Pyran **1b** [21, 22] Yield: 72%. Mp: 219 °C. IR (ν_{max} , cm^{-1}): 3417, 3321, 2193 cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6 + CDCl_3) δ : 7.40 (br, s, 2H), 7.18–8.04 (m, 9H), 5.16 (s, 1H).

Scheme 2 Synthesis of starting materials **4**, **5** and **6**

2.1.3 Synthesis of 2-Amino-3-Cyano-4-Methylfuran **2**

Acetol (3.7 g, 50 mmol) was dissolved in methanol (20 mL) with stirring under an atmosphere of nitrogen and a mixture of malononitrile (3.5 g, 53 mmol) and triethylamine (6.96 mL, 0 mmol) in methanol (25 mL) was added slowly drop-wise at such a rate as to maintain the reaction temperature below 0 °C. After, the reaction mixture was diluted with water (50 mL) and extracted with methylene chloride (2 × 50 mL). The organic layers were combined, dried (MgSO₄) and condensed to a brown solid. Recrystallised from ethyl acetate-hexane gave **2**.

2.1.3.1 2-Amino-3-Cyano-4-Methylfuran **2** [23] Yield: 61%. Mp: 158–159 °C. IR (ν_{max}, cm⁻¹): ν_{NH2} = 3345–3451; ν_{CN} = 2210; ν_{C=C} = 1591. ¹H-NMR (300 MHz, DMSO-*d*₆) δ 6.49 (s, 1H, =CH), 5.76 (br, s, 2H, NH₂), 2.12 (s, 3H, CH₃). ¹³C-NMR (75 MHz, DMSO-*d*₆) δ: 20.2, 24.1, 29.3, 120.4, 127.3, 129.8.

2.1.4 Synthesis of 5-Amino-3-(Methylthio)-1-Phenyl-1H-Pyrazole-4-Carbonitrile **3** [26]

To a mixture of (0.03 mol) of 2-(bis-methylsulfanylmethylene)malononitrile and (0.03 mol) of phenyl hydrazine in (20 mL) ethanol were added drop wise with stirring a solution of diethyl amine or morpholine (2 mL) in ethanol (5 mL). When addition was completed; the mixture was stirred at a temperature of 80 °C to reflux for 9 h. The heating and stirring were still left 1 h. The remaining solids were recrystallized from isopropanol to produce the pure compound **3** (Scheme 1).

2.1.4.1 1-Phenyl-3-(Methylthio)-5-Aminopyrazole-4-Carbonitrile **3** Yield: 81%. Mp: 134–136 °C, ¹H-NMR (300 MHz, DMSO-*d*₆ + CDCl₃) δ: 7.36–7.68 (m, 5H, Ph), 6.21 (br s, 2H, NH₂), 2.67 (s, 3H, SCH₃).

2.1.5 Synthesis of Iminoethers **4**, **5** and **6** [28–30]

A mixture of compounds **1**, **2** and **3** (5 mmol) and excess of ethyl orthoester (10 mL) was heated under reflux for 4–10 h

in the presence of few drops of glacial acetic acid. After removing liberated ethanol and excess of ethyl orthoester under vacuum, we get either a solid that was purified by recrystallization (EtOH) or an oil which was distilled under reduced pressure.

2.1.5.1 *N*-[1-(4-Chloro-Phenyl)-2-Cyano-1H-Benzo[f]chromen-3-yl]-Acetimidic Acid Ethyl Ester 4a Yield: 60%; Mp 109–111 °C; IR (ν_{max} , cm^{-1}) 2200 ($\text{C}\equiv\text{N}$), 1658 ($\text{C}=\text{N}$). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ : 7.19–7.85 (m, 10H, Ar-H); 5.32 (s, 1H), 4.31 (q, $^3J=7.2$ Hz, 2H, OCH_2CH_3), 2.11 (s, 3H, CH_3), 1.37 (t, $^3J=7.2$ Hz, 3H, OCH_2CH_3). ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ : 16.2, 20.1, 25.3, 32.4, 102.6, 110.4, 110.4, 111.9, 111.8, 112.1, 112.8, 116.7, 120.8, 121.0, 131.6, 134.6, 137.5, 141.8, 143.9, 145.4, 148.6, 153.3, 157.3, 163.1.

2.1.5.2 *N*-[1-(4-Chloro-Phenyl)-2-Cyano-1H-Benzo[f]chromen-3-yl]-Propionimidic Acid Ethyl Ester 4b Yield: 95%; Mp 108 °C; IR (ν_{max} , cm^{-1}) 2203 ($\text{C}\equiv\text{N}$), 1652 ($\text{C}=\text{N}$). ^1H NMR (300 MHz, $\text{DMSO}-d_6 + \text{CDCl}_3$) δ : 7.17–7.84 (m, 9H, Ar-H); 5.32 (s, 1H), 4.31 (q, $^3J=7.2$ Hz, 2H, OCH_2CH_3), 2.39 (q, $^3J=7.2$ Hz, 2H, CH_2CH_3), 1.36 (t, $^3J=7.2$ Hz, 3H, OCH_2CH_3), 1.20 (t, $^3J=7.2$ Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ : 17.3, 21.2, 26.4, 32.3, 102.4, 111.6, 111.6, 112.4, 112.4, 113.2, 113.8, 116.5, 121.1, 122.0, 131.4, 133.5, 138.3, 142.4, 143.9, 146.2, 148.7, 154.6, 157.3, 164.2.

2.1.5.3 *N*-[2-(4-Cyano-1-(3,4-Dichloro-Phenyl)-1H-Benzof]chromen-3-yl]-Acetimidic Acid Ethyl Ester 4c Yield: 60%; Mp 114–115 °C; IR (ν_{max} , cm^{-1}) 2214 ($\text{C}\equiv\text{N}$), 1662 ($\text{C}=\text{N}$). ^1H NMR (300 MHz, CDCl_3) δ : 7.13–7.62 (m, 10H, Ar-H), 5.23 (s, 1H), 4.13 (q, $^3J=7.2$ Hz, 2H, OCH_2CH_3), 2.08 (s, 3H, CH_3), 1.41 (t, $^3J=7.2$ Hz, 3H, OCH_2CH_3). ^{13}C NMR (75 MHz, CDCl_3) δ : 17.8, 23.1, 27.1, 34.1, 102.5, 111.7, 111.7, 113.1, 113.1, 113.1, 113.9, 115.6, 123.2, 123.7, 132.8, 137.3, 140.0, 142.7, 144.9, 147.2, 150.2, 153.6, 158.1, 164.1.

2.1.5.4 *N*-[2-(4-Cyano-1-(3,4-Dichloro-Phenyl)-1H-Benzof]chromen-3-yl]-Propionimidic Acid Ethyl Ester 4d Yield: 95%; Mp 116 °C; IR (ν_{max} , cm^{-1}) 2212 ($\text{C}\equiv\text{N}$), 1659 ($\text{C}=\text{N}$). ^1H NMR (300 MHz, $\text{DMSO}-d_6 + \text{CDCl}_3$) δ : 7.23–7.76 (m, 9H, Ar-H); 5.17 (s, 1H), 4.23 (q, $^3J=7.2$ Hz, 2H, OCH_2CH_3), 2.41 (q, $^3J=7.2$ Hz, 2H, CH_2CH_3), 1.31 (t, $^3J=7.2$ Hz, 3H, OCH_2CH_3), 1.18 (t, $^3J=7.2$ Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $\text{DMSO}-d_6 + \text{CDCl}_3$) δ : 18.1, 23.2, 27.2, 32.5, 103.0, 110.7, 110.7, 112.3, 112.3, 112.7, 112.7, 115.6, 121.3, 121.9, 132.1, 133.4, 137.6, 144.6, 145.9, 148.2, 150.4, 154.4, 158.2, 165.7.

2.1.5.5 *N*-(3-Cyano-4-Methyl-Furan-2-yl)-Acetimidic Acid Ethyl Ester 5a Yield: 82%. Mp: 87–88 °C. IR (CHCl_3): 2214, 1645 cm^{-1} . ^1H -NMR (300 MHz, $\text{DMSO}-d_6$) δ : 7.08 (s, 1H), 4.13 (q, $J=7.2$ Hz, 2H, OCH_2CH_3), 2.13 (m, 6H, CH_3), 1.37 (s, 3H). ^{13}C -NMR (75 MHz, $\text{DMSO}-d_6$) δ : 18.1, 22.3, 26.7, 60.3, 116.8, 125.2, 128.6, 140.1, 150.3, 165.7.

2.1.5.6 *N*-(3-Cyano-4-Methyl-Furan-2-yl)-Propionimidic Acid Ethyl Ester 5b Yield: 82%. Mp: 108–109 °C. IR (CHCl_3): 2214 and 1645 cm^{-1} . ^1H -NMR (300 MHz, $\text{DMSO}-d_6$) δ : 6.76 (s, 1H), 3.87 (q, $J=7.2$ Hz, 4H, CH_2), 2.34 (s, 3H, CH_3), 1.41 (t, 6H). ^{13}C -NMR (75 MHz, $\text{DMSO}-d_6$) δ : 16.6, 16.8, 22.3, 30.3, 62.6, 115.7, 123.5, 128.3, 141.3, 151.7, 165.9.

2.1.5.7 *N*-(4-Cyano-5-Methylsulfanyl-2-Phenyl-2H-Pyrazol-3-yl)-Acetimidic Acid Ethyl Ester 6a Yield: 81%, Mp: 94 °C, ^1H -NMR (CDCl_3): $\delta=7.26$ –7.74 (m, 5H, Ph), 4.13 (q, 2H, $\text{O}-\text{CH}_2-\text{CH}_3$), 3.31 (s, 3H, $-\text{SCH}_3$), 3.23 (q, 3H, $\text{O}-\text{CH}_2-\text{CH}_3$). 1.31 (s, 3H, CH_3). ^{13}C -NMR (75 MHz, $\text{DMSO}-d_6 + \text{CDCl}_3$): 18.35, 25.26, 42.31, 103.31, 113.2, 113.6, 113.85, 115.59, 126.7, 126.9, 137.15, 140.12; 140.7, 148.05; 151.38.

2.1.5.8 *N*-(4-Cyano-5-Methylsulfanyl-2-Phenyl-2H-Pyrazol-3-yl)-Propionimidic Acid Ethyl Ester 6b Yield: 81%, Mp: 102 °C, ^1H -NMR (300 MHz, $\text{DMSO}-d_6 + \text{CDCl}_3$): $\delta=7.26$ –7.74 (m, 5H, Ph), 4.26 (q, 2H, $\text{O}-\text{CH}_2-\text{CH}_3$), 2.46–2.50 (s, 3H, $-\text{SCH}_3$), 2.6 (s, 3H, $-\text{CH}_3$), 2.21 (m, 2H, $-\text{CH}_2-\text{CH}_3$), 1.36 (m, 6H, $-\text{CH}_3$). ^{13}C -NMR (75 MHz, $\text{DMSO}-d_6 + \text{CDCl}_3$): 17.17, 18.24, 24.38, 42.52, 102.63, 113.47, 113.76, 113.87, 115.71, 125.8, 126.0, 138.23, 141.31; 141.73, 149.12; 153.21.

2.1.6 Synthesis of Naphtopyranotriazolopyrimidines 7

A mixture of **4** (20 mmol) and hydrazine hydrate (5 mL) in ethanol (15 mL) was refluxed during 7 h, and then left to cool. The solid obtained was collected by filtration and purified by recrystallization from toluene (Scheme 2), washed with ethanol, dried and crystallized from ethanol to give pale yellow crystals 4-iminopyranopyrimidine **7'**. To a solution of compounds **7'** (10 mmol) in Toluene (50 mL) containing TsOH (0.1 g) as catalyst, was added ethyl cyanoacetate (10 mmol). The reaction mixture was heated under reflux overnight. The mixture was then poured onto ice/water and the formed solid pyranotriazolopyrimidine derivatives **7** collected by filtration and recrystallized from ethanol/water.

2.1.6.1 2-Cyanomethyl-5-Methyl-1-(4-Chloro-Phenyl)-1H-Benzo[f]Chromene[3,2e][1,2,4]Triazolo[1,5-c]Pyrimidine 7a Yield: 77%. Mp: 202–204 °C. IR: 3081, 2972, 2211, 1656, 1630, 1587, 1571, 1453, 771, 743 cm^{-1} . ^1H -NMR (300 MHz, $\text{CDCl}_3 + \text{DMSO-d}_6$) δ : 7.56–7.37 (m, 10H), 6.42 (s, 1H), 4.18 (s, 2H), 2.54 (s, 3H). ^{13}C NMR (75 MHz, $\text{DMSO-d}_6 + \text{CDCl}_3$) δ : C_1 , 20.4; C_2 , 31.6; C_4 , 30.2; C_6 , 102.2, C_7 , 114.3, C_8 , 117.6, C_5 , 123.5, C_9 – C_{14} , 125.3, 127.5, 128.5, C_{15} – C_{20} , 128.7, 130.2, 130.2, 131.2, 131.6, C_{21} , 142.0, C_{22} , 148.0, C_{23} , 149.8, C_{24} , 156.1, C_{25} , 157.7, C_{26} , 160.9. Anal. Calcd for ($\text{C}_{25}\text{H}_{15}\text{ClN}_5\text{O}$) 436.8805: C, 68.732; H, 3.461; N, 16.031. Found: C, 68.72; H, 3.48; N, 16.01.

2.1.6.2 2-Cyanomethyl-5-Ethyl-1-(4-Chloro-Phenyl)-1H-Benzo[f]Chromene[3,2e][1,2,4]Triazolo [1,5-c]Pyrimidine 7b Yield: 84%. Mp: 180–181 °C. IR: 3093, 2983, 2221, 1645, 1620, 1596, 1574, 1450, 771, 728 cm^{-1} . ^1H -NMR (300 MHz, $\text{CDCl}_3 + \text{DMSO-d}_6$) δ : 7.84–8.13 (m, 10H), 6.74 (s, 1H), 4.21 (s, 2H), 2.57 (s, 3H), 1.29 (t, 3H, $J = 7.2$). ^{13}C NMR (75 MHz, $\text{DMSO-d}_6 + \text{CDCl}_3$) δ : C_1 , 18.7, C_2 , 25.1, C_3 , 32.4, C_4 , 32.2; C_6 , 102.2, C_7 , 114.3, C_8 , 117.6, C_5 , 123.5, C_9 – C_{14} , 125.3–128.5, C_{15} – C_{20} , 128.7–131.6, C_{21} , 141.5, C_{22} , 142.1, C_{23} , 149.2, C_{24} , 149.8, C_{25} , 155.7, C_{26} , 157.6. Anal. Calcd for ($\text{C}_{26}\text{H}_{18}\text{ClN}_5\text{O}$) 450.9073: C, 69.257; H, 3.8; N, 15.532. Found: C, 69.30; H, 3.76; N, 15.49.

2.1.6.3 2-Cyanomethyl-5-Methyl-1-(3,4-Dichloro-Phenyl)-1H-Benzo[f]Chromene[3,2e][1,2,4]Triazolo [1,5-c]Pyrimidine 7c Yield: 81%. Mp: 217–219 °C. IR: 3057, 2977, 2218, 1661, 1632, 1583, 1568, 1454, 781, 732 cm^{-1} . ^1H -NMR (300 MHz, $\text{CDCl}_3 + \text{DMSO-d}_6$) δ : 7.69–7.48 (m, 9H), 6.46 (s, 1H), 4.27 (s, 2H), 2.48 (s, 3H). ^{13}C NMR (75 MHz, $\text{DMSO-d}_6 + \text{CDCl}_3$) δ : C_1 , 17.1, C_2 , 31.7, C_4 , 29.8; C_6 , 109.7, C_7 , 113.5, C_8 , 119.2, C_5 , 120.1, C_9 – C_{14} , 127.6–128.1; C_{15} – C_{20} , 132.4–137.6; C_{21} , 143.2, C_{22} , 145.1, C_{23} , 148.7, C_{24} , 154.9, C_{25} , 156.6, C_{26} , 164.5. Anal. Calcd for ($\text{C}_{25}\text{H}_{15}\text{Cl}_2\text{N}_5\text{O}$) 471.3256: C, 63.709; H, 2.994; N, 14.859. Found: C, 63.73; H, 3.05; N, 14.81.

2.1.6.4 2-Cyanomethyl-5-Ethyl-1-(3,4-Dichloro-Phenyl)-1H-Benzo[f]Chromene[3,2e][1, 2, 4]Triazolo[1,5-c]Pyrimidine 7d Yield: 78%. Mp: 202–204 °C. IR: 3097, 2981, 2220, 1648, 1623, 1589, 1571, 1452, 783, 734 cm^{-1} . ^1H -NMR (300 MHz, $\text{CDCl}_3 + \text{DMSO-d}_6$) δ : 7.93–8.11 (m, 9H), 6.67 (s, 1H), 4.25 (s, 2H), 2.56 (s, 3H), 1.32 (t, 3H, $J = 7.2$). ^{13}C NMR (75 MHz, $\text{DMSO-d}_6 + \text{CDCl}_3$) δ : C_1 , 20.7, C_2 , 26.3, C_3 , 35.1, C_4 , 103.3, C_6 , 116.0, C_7 , 118.5, C_8 , 122.7, C_5 , 125.4, C_9 – C_{14} , 127.3–128.5, C_{15} – C_{20} , 131.2–137.0, C_{21} , 145.7, C_{22} , 147.3, C_{23} , 151.8, C_{24} , 153.7, C_{25} , 159.2, C_{26} , 164.3. Anal. Calcd for ($\text{C}_{26}\text{H}_{17}\text{Cl}_2\text{N}_5\text{O}$) 485.3524: C, 64.342; H, 3.323; N, 14.43. Found: C, 64.38; H, 3.29; N, 14.47.

2.1.7 Synthesis of 2-Cyanomethyl-Methylfuro[3,2-e][1,2,4]Triazolo[1,5-c]Pyrimidine 8 and 9

The method of preparation of these furotriazolopyranopyrimidines **8** and or **9** is the following. To a mixture of dry toluene (200 mL), Iminoether **5** or **6** (2.96 g, 10 mmol) and Para-toluene sulfonic acid (0.1 g) as catalyst was added cyanoacetic acid hydrazide (10 mmol). The mixture was heated under reflux in a Dean–Stark apparatus with removal of water and ethanol formed during 21–27 h. Evaporation of most of toluene left a residue which was dissolved in 20 mL of saturated solution of sodium bicarbonate and then extracted twice with 25 mL of chloroform. The organic layers was washed with 25 mL of saturated sodium chloride solution and then with 30 mL of distilled water and then dried over MgSO_4 . After removal of chloroform, the solid obtained was filtered and recrystallized from ethanol.

2.1.7.1 (5,9-Dimethyl-Furo[3,2,e][1,2,4]Triazolo[1,5-c]Pyrimidin-2-yl)-Acetonitrile 8a Yield: 67%. Mp: 145 °C. IR: 3076, 2987; 2221; 1651, 1621. ^1H -NMR (300 MHz, DMSO-d_6) δ : 2.96 (s, 3H, CH_3); 4.74 (s, 2H, CH_2); 6.45 (s, 1H). ^{13}C -NMR (75 MHz, DMSO-d_6) δ : C_1 , 20.7, C_2 , 22.5, C_3 , 23.1; C_5 , 114.8; C_7 , 117.1; C_6 , 120.8, C_8 , 138.2, C_9 , 141.9, C_{10} , 148.8, C_{11} , 157.3, C_{12} , 164. Anal. Calcd for ($\text{C}_{11}\text{H}_9\text{N}_5\text{O}$) 227.2261: C, 58.145; H, 3.992; N, 30.822. Found: C, 58.08; H, 4.12; N, 30.71.

2.1.7.2 (5-Ethyl-9-Methyl-Furo[3,2,e][1,2,4]Triazolo[1,5-c]Pyrimidin-2-yl)-Acetonitrile 8b Yield: 65%. Mp: 167 °C. IR: 3083, 3000; 2223; 1646, 1627. ^1H -NMR (300 MHz, DMSO-d_6) δ : 1.42 (t, 3H, CH_3), 3.37 (q, 2H, CH_2); 4.76 (s, 2H, CH_2); 6.73 (s, 1H). ^{13}C -NMR (75 MHz, DMSO-d_6) δ : C_1 , 20.7, C_2 , 22.1, C_3 , 22.5; C_4 , 26.4, C_5 , 116.1; C_7 , 117.4; C_6 , 120.3, C_8 , 139.5, C_9 , 143.2, C_{10} , 150.8, C_{11} , 158.7, C_{12} , 168.6. Anal. Calcd for ($\text{C}_{12}\text{H}_{11}\text{N}_5\text{O}$) 241.2529: C, 59.743; H, 4.596; N, 29.03. Found: C, 59.78; H, 4.51; N, 29.21.

2.1.7.3 (5-Methyl-9-Methylsulfanyfuryl-7H-Pyrazolo[4,3-e][1,2,4]Triazolo[1,5,c]Pyrimidin-2-yl)-Acetonitrile 9a Yield: 76%. Mp: 246–248 °C. IR: 3093, 2984; 2223; 1646, 1627. ^1H -NMR (300 MHz, $\text{DMSO-d}_6 + \text{CDCl}_3$) δ : 2.40 (s, 3H, CH_3), 3.23 (s, 3H, S-CH_3), 3.58 (s, 2H), 7.35–7.76 (m, 5H, Ar-H, $J = 7.2$ Hz). ^{13}C -NMR (75 MHz, $\text{DMSO-d}_6 + \text{CDCl}_3$) δ : C_1 , 17.3, C_2 , 21.6, C_3 , 22.2, C_5 , 114.8, C_6 , 120.7, C_7 – C_{12} , 123.6–130.5, C_{13} , 140.2, C_{14} , 142.3, C_{15} , 147.4, C_{16} , 161.6, C_{17} , 165.8. Anal. Calcd for ($\text{C}_{16}\text{H}_{13}\text{N}_7\text{S}$) 335.3937: C, 57.299; H, 3.907; N, 29.234. Found: C, 57.30; H, 4.08; N, 29.26.

2.1.7.4 (5-Ethyl-9-Methylsulfonyl-7H-Pyrazolo[4,3-e][1,2,4]Triazolo[1,5,c]Pyrimidin-2-yl)-Acetonitrile 9b Yield: 70%. Mp: 253–255 °C. IR: 3081, 2991; 2218; 1652, 1632. ^1H -NMR (300 MHz, $\text{DMSO-d}_6 + \text{CDCl}_3$) δ : 1.26 (t, 3H, $J=7.2$), 3.18 (s, 3H, SCH_3), 2.65 (q, 2H, $J=7.2$), 3.67 (s, 2H), 7.35 (d, 5H, Ar-H, $J=7.2$ Hz). ^{13}C -NMR (75 MHz, $\text{DMSO-d}_6 + \text{CDCl}_3$) δ : C_1 , 18.5, C_2 , 21.3, C_3 , 23.7, C_4 , 31.2; C_5 , 113.9, C_6 , 118.7, C_7 – C_{12} , 124.3–131.7, C_{13} , 142.6, C_{14} , 144.1, C_{15} , 148.7, C_{16} , 163.4, C_{17} , 168.1. Anal. Calcd for ($\text{C}_{17}\text{H}_{15}\text{N}_7\text{S}$) 349.4205: C, 58.436; H, 4.327; N, 28.06. Found: C, 58.44; H, 4.28; N, 28.19.

2.2 Antibacterial Screening for Furo, Pyrano, and Pyrazolo[3,2,e][1,2,4]Triazolo-[1,5-c]Pyrimidine 7, 8 and 9

Compounds **7a–c**, **8a–b** and **9a–b** were examined for their antibacterial activity with paper disc ($\phi 5$ mm) method as described by [33–35] and compared with that of Tetracycline (TE_{30} , 54882, 30 μg), considered as reference. Strains used as test organisms in this study were; *Salmonella typhimurium* (ATCC14028: Source Département de génétique, Faculté de biologie, Université de Seville, Seville 41080, Espagne) *Pseudomonas aeruginosa* (Centre technique de l'agroalimentaire de Tunis) *Escherichia coli* (JW 1772) and *Staphylococcus aureus* (Centre technique de l'agroalimentaire de Tunis). Briefly, Tested compounds **7a–c**, **8a–b** and **9a–b** were dissolved in a DMSO at different concentrations (1–54 M) as well as reference antibiotics TE_{30} (21 mg/mL). Paper discs were soaked in each compound solution for 3–5 min a then transferred into the surface of growth media seeded with the test organism. After an incubation period (24 h at 35 °C), the diameters of the inhibition zones around the discs were measured (mm). Standard blank with no added test compounds was also analyzed. The obtained results are summarized in Tables 2 and 3. Table 3 summarizes the TE_{30} diameter of the inhibition zones against studied bacteria strains in a dimethylsulfoxide (DMSO).

3 Results and Discussion

3.1 Synthesis

The synthetic route of the triazolopyrimidines **7**, **8**, and **9** is outlined in the Schemes 2, 3 and 4. “2-Amino-3-cyano-4-methylfuran **1**, 2-amino-3-cyano-pyrans **2**, 1-Phenyl-3-thiomethyl-5-aminopyrazole-4-carbonitrile **3**” were selected as our primary starting material for this synthesis and were prepared by methods taken from the literature [21–23], the reactivity of the cyanoacetic acid hydrazone has been already reported by the present authors [24, 28]. Compound

1, **2** and **3** reacted with excess of ethyl orthoester to yield iminoethers **4**, **5** and **6** (Scheme 2), which were known to react with compounds containing $-\text{NH}_2$ moiety such as hydrazides [4, 25–29].

In fact these precursors possess two reactive sites, a cyano group and an imidic carbon. These groups render them susceptible to react with cyanoacetic acid hydrazide in refluxing toluene with catalytic amount of *p*-toluenesulfonic acid to afford triazolopyrimidines **7**, **8** and **9**. From the mechanistic view point and as shown in Scheme 1, two plausible pathways and different intermediates and products could be expected. Indeed, the bis electrophilic character of iminoether **4** would allow a successive two nucleophilic additions of $-\text{NH}_2$ group or of $\text{NH}_2-\text{NH}-$ moiety on the imidic carbon and the cyano group, which would give by intracyclisation via elimination of water to compound **7**, and which was isolated in some cases when ethanol was used as solvent or amidopyranopyrimidines **7'**. Based on spectral data, the reaction was proceeded to produce pyranotriazolopyrimidine derivatives **7** rather than amidopyranopyrimidines **7'**. But iminoethers **5** and **6** would allow a successive two nucleophilic additions of $-\text{NH}_2$ group or two nitrogen of $\text{NH}_2-\text{NH}-$ moiety on the imidic carbon and the cyano group, which would give respectively their intermediate (furano and pyrazolo)triazepines **8'**, **9'** and/or their isomers **8''**, **9''** that can be evolved by intramolecular cyclization via elimination of water to compounds furo(pyrazolo)triazolopyrimidine derivatives **8** and **9** (Scheme 3, Fig. 1, Table 1).

A plausible mechanism for the formation of triazolopyrimidines **7**, **8** and **9** is depicted in Scheme 4. The transformation is believed to proceed via the nucleophilic attack of $-\text{NH}_2$ group on the imidic carbon and the cyano group, giving rise to an imine intermediate. A subsequent intramolecular cyclization through the nucleophilic attack of the imino group on the carbonyl of the amide group, leads to the final.

4 DFT Study

4.1 Computational Method

Gaussian 09 has been employed for all the theoretical calculations [30]. Geometries of the molecules **7'**, **8'** and **9'** were optimized using the DFT at B3LYP level [31–34] along with 6–31G(d, p) basis set. The molecule **7'** was calculated without $-\text{Cl}$ in order to reduce the computational calcul. Stable minima of Ground state S0 geometries were confirmed by the absence of imaginary frequencies in the subsequent vibrational frequency calculations. The vibrational spectra of the compounds studied were calculated at the B3LYP/6–31G(d, p) optimized geometries. The torsional barriers around the $\text{N}_7-\text{N}_6-\text{C}_4-\text{C}_3$ and $\text{N}_{19}-\text{N}_{20}-\text{C}_{21}-\text{C}_{22}$ dihedral angle have been investigated with B3LYP/3–21G(d)

Scheme 3 Synthetic route for the title compounds **7**, **8** and **9**

Scheme 4 A plausible mechanism for the formation of triazolopyrimidines **7**, **8** and **9**

Fig. 1 Triazolopyrimidines **7**, **8** and **9**

for both compound **8'** and **9'** respectively (Figures). UV–Vis spectral was investigated at *TD-B3LYP/6–31G(d, p)* [19, 20]. All calculations were performed in the gas phase.

4.2 Molecular Geometry

Naphtopyrano, furo and pyrazolotriazolopyrimidine derivatives **7**, **8** and **9** can theoretically exist in form conformational isomers represented below (Fig. 2) and make appear different types of intramolecular hydrogen bonds.

It should be noted that the analysis spectra of compounds **7'**, **8'** and **9'** carried out in $CDCl_3$ have a single isomer alone; one of the three conformations is preferred. In order to

determine the most stable conformation under which these compounds exist, a theoretical study carried out on compounds **7'**, **8'** and **9'** using the *Gaussian 09* program carried out at the *DFT (Functional Density Theory)* level with the functional *B3LYP29* was undertaken.

According to Brown's criterion, there are three classes of hydrogen bonds. Very strong, strong and weak depending on the distances and angles shown in the Table 2.

The existence of hydrogen bonding for these compounds is due to the presence of adjacent amide group, amino group and nitrile group in the aromatic ring. To know the impact of hydrogen bonding in defining conformational flexibility

Table 1 Prepared synthesized triazolopyrimidines **7**, **8** and **9**

7, 8 and 9	Ar	R	Time (h)	Yield (%)*
7a		Me	28	77
7b		Et	26	84
7c		Me	23	81
7d		Et	25	78
8a	-	Me	20	67
8b	-	Et	24	65
9a	-	Me	26	76
9b	-	Et	22	70

*Yield calculated using the reaction of scheme (2)

of the molecule, B3LYP/3–21G(d) calculations were carried out by applying rotations (Fig. 3).

The stable molecule corresponds to minimum energy using potential energy scan [35]. The relative energy

Fig. 2 different types of intra-molecular hydrogen bonds of triazolopyrimidines **7**, **8** and **9**

Table 2 Classes of hydrogen bonds

Classes Distances and angles	Very strong H–A≡D–H	Strong H...A>D–H	Weak H...A≫D–H
d (H...A) (Å)	1.2–1.5	1.5–2.2	> 2.5
∠ (D–H...A) (°)	175–180	130–180	90–180

of the three molecules was calculated at *B3LYP/6–31G* (*d*). It was found that the molecule **9'** was the most stable. The energies of the others were $-3,645,013.145$ and $-2,231,583.532$ kJ mol $^{-1}$ for molecule **7'** and **8'**, respectively (Table 3).

The torsional barrier of molecule **8'** showed that C₄=O₅ and N₆–H₁₆ were on the same side (Fig. 4). This result leads to the formation of intramolecular hydrogen O₅...H₁₆–N₆.

The torsional barrier of molecule **9'** showed that N₁₉–N₂₀–C₂₁–C₂₂ dihedral angle was 2.57 Å (Fig. 5).

The fully optimized molecular structures of molecules **7'** and **8'** with atomic numbering, calculated at *B3LYP/6–31G* (*d,p*) level of the theory, are shown in Fig. 1. Selected calculated bond distances are given in Table 3. As seen from Table 4. Two intramolecular hydrogen O₅...H₁₆–N₆ and

Table 3 The relative energies of compounds **7'**, **8'** and **9'**

<i>B3LYP</i> <i>6-31G(d,p)</i>	Molecule 7' _{II}	Molecule 8' _{III}	Molecule 9' _{III}
Energy/ kJ mol $^{-1}$	$-3,645,013.145$	$-2,231,583.532$	$-3,873,610.11$

N₆...H₁₅–N₁₄ for molecules were found. The presence of intramolecular Hydrogen significantly lowers the energy of the system and stabilizes the molecule. The stabilization of molecule is matched with the shortening of O₅...H₁₆–N₆ and N₆...H₁₅–N₁₄ distance. From the results of Table 3, it was observed that the calculated C₄=O₅ and H₁₅–N₁₄ bond distances of the molecule **9'** reduced. This result showed that –S–CH₃ was responsible for the reduced of C₄=O₅ and H₁₅–N₁₄ bond distances.

4.3 Electronic Structure and UV Spectrum

TD-B3LYP/6–31G (*d,p*) based on *B3LYP/6–31G* (*d,p*) geometries was used to determine the low lying excited state of the molecule. Excitation energy, oscillator strength, and the main components of the ground state S₀→excited

Fig. 3 Optimized structure at *B3LYP/6-31G(d,p)*

Fig. 4 Torsional barrier of molecule **8'** around the N–N–C–C dihedral angle at B3LYP/3–21G(d)

Fig. 5 Torsional barrier of molecule **9'** around the N–N–C–C dihedral angle at B3LYP/3–21G(d)

Table 4 Geometrical parameters of molecule **7'**, **8'** and **9'**

Bond length (Å°)	Molecule-7' _{II}	Molecule-8' _{III}	Molecule-9' _{VI}
N1...H15	5.413	5.397	5.435
N1...H16	5.551	5.556	5.539
O5...H16	2.44	2.450	2.448
N6...H15	2.375	2.38	2.343
O5...H15	3.275	3.316	3.311
S18...H15			4.562
C4=O5	1.210	1.211	1.210
N6–H16	1.015	1.015	1.015
H15–N14	1.019	1.020	1.019

state S_1 transition energy of each system are summarized in Table 5. The lowest excited states of the investigated structures is characterized by $\pi \rightarrow \pi^*$ transition from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO). The $\pi \rightarrow \pi^*$ transition was observed for two molecule and caused by C=O in amide group. The excitation energies decrease from 4.178 eV for the molecule **8'** to 3.689 eV for the molecule **9'**. The main absorption peak of molecule **8'** is blue-shifted with respect to the one of molecule **9'** and **7'** (Fig. 6).

Table 5 Calculated maximum absorption wavelength (λ), excitation energies (E), oscillator strength (f) of molecule **7'**, **8'** and **9'** by the TD-DFT method

	Calculated wave-length	Energy (eV)	Oscillator strength	Transition
Molecule 7'	336.49	3.684	0.0167	H $\rightarrow$ L (97.13%)
Molecule 8'	296.71	4.178	0.1997	H $\rightarrow$ L (97.82%)
Molecule 9'	336.06	3.689	0.1066	H $\rightarrow$ L (97.016%)

Fig. 6 Calculated UV–Vis spectra of different molecules at TD-DFT

4.4 The Frontier Molecular Orbitals of Molecules **7'**, **8'** and **9'**

The interested orbital in molecules are the frontier molecular orbital, highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO). Specific molecular orbital MO localization can be introduced by donor–acceptor molecules, while (LUMO) is localized on the acceptor unit and the (HOMO) is localized on the donor unit (Fig. 7).

The stabilization in (LUMO) is more pronounced than the stabilization in (HOMO), so that molecule **7'** and **9'** have smaller (HOMO–LUMO) gaps as compared to the molecule **8'** (Table 6).

4.5 Infrared Spectroscopy

ATR-FTIR spectra of compounds **8'** and **9'** are presented in Fig. 8. They show the presence of two characteristic bands of the NH of the amin group and a broad band centered at 3344 and 3246 cm^{-1} associated with the $2 \times \text{N-H}$ stretching

vibration, and an intense band at around 1680 cm^{-1} assigned to the vibration of the C=O group. The spectra exhibited also a decrease of the intensities of the bands at 1450 cm^{-1} , 1498 cm^{-1} and 1607 cm^{-1} attributed to the C=C groups in the benzene ring. The CN stretching was observed at 2219 cm^{-1} . The imine (CH=N) vibration corresponding to Schiff base formation was newly observed at 1622 cm^{-1} [28].

The experimental results were combined with theoretical data which describes molecular features. In computational studies, DFT method was also used to compute geometrical parameters, (HOMO) and (LUMO) energy levels by DFT/B3LYP basis set in Gaussian 09 (Fig. 9) [36].

5 Biological Activity

All the title compounds derivatives **7a–c**, **8a–b** and **9a–b** were tested for their antibacterial activity Gram positive and Gram negative against four types of Bacteria and was measured by measuring the zone of inhibition in disc diffusion method (Table 7).

Fig. 7 B3LYP-calculated wave functions of the frontier molecular orbitals of molecules 7', 8' and 9'

Table 6 Calculated HOMO, LUMO and energy gap E_{L-H} in eV at B3LYP/6–31G(d)

	HOMO	LUMO	E_{L-H}
Molecule 7'	– 5.880	– 1.6035	4,2765
Molecule 8'	– 6.0385	– 1.4005	4638
Molecule 9'	– 5.941	– 1.697	4244

The antibacterial activity was tested with the disc methods according to against *Staphylococcus Pseudomonas*, *Escherichiacoli* and *Salmonella*. This test is summarized by a resistance study of different compounds and standard

antibiotic Tetracycline TE₃₀. The colony diameter was noted after 3 days of incubation at 25 °C. Control received the same volume of sterilized distilled water. Bacteria growth was measured by averaging the three diameters taken at right angles for each colony. Percentage growth inhibition (%) of bacteria colonies was calculated according to the following formula [37] Growth inhibition (%) = [(Growth in control – Growth in treatment)/Growth in control] × 100: significant inhibition zone (IZ) results was taken in a range of lyses more than 10 mm and the minimum inhibitory concentrations (MIC) has been calculated. The highest active products were represented by the minimum inhibitory concentrations (MIC) (Fig. 10).

Fig. 8 ATR-FTIR spectra of compounds 8' and 9'

Results recorded in Table 8 showed the inhibition-diameter of compounds 7a–c, 8a–b and 9a–b and reference TE₃₀. Our results show that furano, pyrano, and pyrazolotriazolo-pyrimidine exhibited a moderate antibacterial activity

against both Gram-positive and Gram-negative bacteria [38]. Importantly, pyranotriazolopyrimidine, 8a did not show any significant antibacterial activity against all used strains (> 36 mg/mL) and no lyses plaque was observed with all concentrations used. Accordingly, compound 8b inactivate *Staphylococcus* and *Salmonella* with a high MIC (34.46 mg/mL) whereas compound 9a and 9b seems to be more effective with a low MIC and a good IZ. With regard to the mechanism of antibacterial activity, one can speculate that compound 8b is not able to diffuse intracellular and to inhibit bacterial peptidoglycan. We note that adding a CH₃ or CH₂–CH₃ in the fragment R decreases the activity. Furthermore, we noted that pyrazolotriazolopyrimidine 9a and 9b showed an inhibition zone at about 5 and 6.5 mm against *Staphylococcus*. This result may be probably related to the presence of the phenyl group. Interestingly, compound 7a and 7c showed the highest inhibition zone at around 16 mm against *Staphylococcus* and *Pseudomonas*. This result may be attributed to the presence of dihydronaphtho group [39–43] in the R ring. It is important to mention that all tested compounds, except 7a and 7c showed a low antibacterial activity in comparison to TE₃₀ as can be noticed from Table 3.

6 Conclusions

In conclusion, a new series of naphthopyrano, furo and pyrazolo[3,2,e][1,2,4]triazolo-[1,5-c]pyrimidine 7a–c, 8a–b and 9a–b were synthesized and the structure was characterized on the basis of their infrared (IR), NMR spectral data. All the title compounds were tested for their antibacterial

Fig. 9 ATR-FTIR spectra of compounds 8' and 9'

Table 7 Prepared synthesized of compounds **7(a,c)**, **8(a,b)** and **9(a,b)**

compounds 7	compounds 8	compounds 9
<p>7a</p>	<p>8a</p>	<p>9a</p>
<p>7c</p>	<p>8b</p>	<p>9b</p>

Fig. 10 Figures discs containing products synthesized by different concentrations

activity against four types of Bacteria. According to the results obtained, compounds **7a–c**, **8a–b** and **9a–b** exhibited a moderate in vitro antibacterial activity compared to the

TE₃₀ reference. Naphthotriazolopyrimidine **7a** and **7c** showed the highest antibacterial activity. This can be attributed to the dihydronaphtho group.

Table 8 Antibacterial activity of compounds **7(a,c)**, **8(a,b)** and **9(a,b)** as inhibition diameter or IZ Diameters (mm) and minimal inhibition concentration MIC (mg/mL)

	Gram+		Gram–					
	<i>Staphylococcus</i>		<i>Pseudomonas</i>		<i>Escherichia</i>		<i>Salmonella</i>	
	(mg/mL)	(mm)	(mg/mL)	(mm)	(mg/mL)	(mm)	(mg/mL)	(mm)
7a	16.74	15.56	16.74	14.78	–	–	–	–
7c	18.53	16.13	18.53	15.11	–	–	–	–
8a	36.67	3.52	36.67	2.63	–	–	36.67	1.57
8b	34.46	4.06	34.46	3.83	–	–	34.46	3.14
9a	18.92	5	18.92	5	–	–	–	–
9b	16.52	6.5	16.52	6.5	–	–	–	–
TE30 (30 µg)	21	26	21	21	21	24	21	22

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

- Wang XS, Yang GS, Zhao G (2008) Enantioselective synthesis of naphthopyran derivatives catalyzed by bifunctional thiourea-tertiary amines. *Tetrahedron Asymmetry* 19(6):709–714. <https://doi.org/10.1016/j.tetasy.2008.02.018>
- Fakher C, Mehdi M, Hédi BM, Leila CG, Mansour S (2007) Synthesis and antigenotoxic activity of some naphtho[2,1-b]pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine derivatives. *Eur J Med Chem* 42(5):715–718. <https://doi.org/10.1016/j.ejmech.2006.12.002>
- Mutchu BR, Kotra V, OntedduSR Boddapati SNM, Bollikolla HB (2019) Synthesis, cytotoxicity and antimicrobial evaluation of some new 2-Aryl,5-substituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles. *Chem Afr* 2:15–20. <https://doi.org/10.1007/s42250-018-00034-x>
- Mantoani SP, Chierrito TPC, Vilela AFL, Cardoso CL, Martínez A, Carvalho I (2016) Novel triazole-quinoline derivatives as selective dual binding site acetylcholinesterase inhibitors. *Molecules* 21(2):193. <https://doi.org/10.3390/molecules21020193>
- Bedair AH, Emam HA, El-Hady NA, Ahmed KAR, El-Agrody AM (2001) Synthesis and antimicrobial activities of novel naphtho[2,1-b]pyran, pyrano[2,3-d]pyrimidine and pyrano[3,2-e][1,2,4]triazolo[2,3-c]-pyrimidine derivatives. *ILFarmaco* 56(12):965–973. [https://doi.org/10.1016/S0014-827X\(01\)01168-5](https://doi.org/10.1016/S0014-827X(01)01168-5)
- Amole KL, Bello IA, Oyewale AO (2019) Synthesis, characterization and antifungal study of five new derivatives of E-1-(--hydroxyphenyl)chalcone. *Chem Afr* 2:1–14. <https://doi.org/10.1007/s42250-018-0027-3>
- Musiol R, Jampilek J, Buchta V, Silva L, Niedbala H, Podeszwa B, Palka A, Majerz-Maniecka K, Oleksyn B, Polanski J (2006) Antifungal properties of new series of quinoline derivatives. *Bioorg Med Chem* 14(10):3592–3598. <https://doi.org/10.1016/j.bmc.2006.01.016>
- Johnson TC, Martin TP, Mann RK, Pobanz MA (2009) Penoxulam structure activity relationships of triazolopyrimidine sulfonamides. *Bioorg Med Chem* 17(12):4230–4240. <https://doi.org/10.1016/j.bmc.2009.02.010>
- Bruno O, Brullo C, Schenone S, Bondavalli F, Ranise A, Tognolini M, Ballabeni V, Barocelli E (2004) Synthesis and pharmacological evaluation of 5H-[1]benzopyrano[4,3-d]pyrimidines effective as antiplatelet/analgesic agents. *Bioorg Med Chem* 12(3):553–561. <https://doi.org/10.1016/j.bmc.2003.11.018>
- Rashad AE, Heikal OA, Elnezhawy AOA, Abdelmegeid FM (2005) Synthesis and isomerization of thienotriazolopyrimidine and thienotetrazolopyrimidine derivatives with potential anti-inflammatory activity. *Heteroat Chem* 16(3):226–234. <https://doi.org/10.1002/hc.20114>
- Chen WB, Jin GY (2003) Syntheses and biological activities of S-1,2,4-triazolo (1,5-a) pyrimidinylalkyl dithiophosphates. *Heteroat Chem Int J Main Group Elements* 14(7):607–611. <https://doi.org/10.1002/hc.10198>
- Martin-Köhler A, Widmer J, Bold G, Meyer T, Sequin U, Traxler P (2004) Furo [2,3-d] pyrimidines and oxazolo [5,4-d] pyrimidines as inhibitors of receptor tyrosine kinases (RTK). *Helv Chim Acta* 87(4):956–975. <https://doi.org/10.1002/hlca.200490089>
- Isloor AM, Kalluraya B, Shetty P (2009) Regioselective reaction: synthesis, characterization and pharmacological studies of some new Mannich bases derived from 1,2,4-triazoles. *Eur J Med Chem* 44(9):3784–3787. <https://doi.org/10.1016/j.ejmech.2009.04.038>
- Kumar R, Nair RR, Dhiman SS, Sharma J, Prakash O (2009) Organiodine (III)-mediated synthesis of 3-aryl/heteroaryl-5,7-dimethyl-1,2,4-triazolo [4,3-c] pyrimidines as antibacterial agents. *Eur J Med Chem* 44(5):2260–2264. <https://doi.org/10.1016/j.ejmech.2008.06.004>
- Bruno O, Brullo C, Schenone S, Bondavalli F, Ranise A, Tognolini M, Barocelli E (2006) Synthesis, antiplatelet and antithrombotic activities of new 2-substituted benzopyrano [4,3-d] pyrimidin-4-cycloamines and 4-amino/cycloamino-benzopyrano [4,3-d] pyrimidin-5-ones. *Bioorg Med Chem* 14(1):121–130. <https://doi.org/10.1016/j.bmc.2005.07.066>
- Savini L, Chiasserini L, Pellerano C, Filippelli W, Falcone G (2001) Synthesis and pharmacological activity of 1,2,4-triazolo [4,3-a] quinolines. *IL Farmaco* 56(12):939–945. [https://doi.org/10.1016/S0014-827X\(01\)01166-1](https://doi.org/10.1016/S0014-827X(01)01166-1)
- Abd El-Wahab AH (2012) Synthesis, reactions and evaluation of the antimicrobial activity of some 4-(p-Halophenyl)-4H-naphthopyran, pyranopyrimidine and pyranotriazolopyrimidine derivatives. *Pharmaceuticals* 5(7):745–757. <https://doi.org/10.3390/ph5070745>
- Dridi K, El Efrat ML, Zantour H (1999) Action d'amines et de derives d'hydrazines sur les N-(3-carboxy-2-thieny) imino ethers: synthese de thieno [2,3-d] pyrimidin-4 (3H)-ones. *J Soc Chim Tunis* 5:387–392

19. Adamo C, Jacquemin D (2013) The calculations of excited-state properties with time dependent density functional theory. *Chem Soc Rev* 42(3):845–856. <https://doi.org/10.1039/c2cs35394f>
20. Gierschner J, Cornil J, Egelhaaf HJ (2007) Optical bandgaps of π -conjugated organic materials at the polymer limit: experiment and theory. *Adv Mater* 19(2):173–191. <https://doi.org/10.1002/adma.200600277>
21. Mkaouer K, Chabchoub F, Samadi A, Marco CJ, Salem M (2011) A novel Synthesis of 14-aryl-14 h-naphto [2,1-b]pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidines. *Heterocycl Lett* 1(2):96–105
22. Gatta F, Del Giudice MR, Borioni A, Borea PA, Dionisotti S, Ongini E (1993) Synthesis of imidazo [1, 2-c] pyrazolo [4, 3-e] pyrimidines, pyrazolo [4, 3-e] 1, 2, 4-triazolo [1, 5-c] pyrimidines and 1, 2, 4-triazolo [5, 1-i] purines: new potent adenosine A2 receptor antagonists. *Eur J Med Chem* 28(7–8):569–576. [https://doi.org/10.1016/0223-5234\(93\)90087-U](https://doi.org/10.1016/0223-5234(93)90087-U)
23. Shaker RM (2006) The chemistry of mercapto-and thione-substituted 1,2,4-triazoles and their utility in heterocyclic synthesis. *Arkivoc* 9:59–112
24. Pyo JI, Hwang EJ, Cheong CS, Lee SH, Lee SW, Kim IT, Lee SH (2005) Synthesis and photoluminescent properties of novel furopyrimidine derivatives. *Synth Met* 155(3):461–463. <https://doi.org/10.1016/j.synthmet.2005.06.017>
25. Wu H, Feng JT, Lin KC, Zhang X (2012) Synthesis and herbicidal activity of substituted pyrazole isothiocyanates. *Molecules* 17(10):12187–12196. <https://doi.org/10.3390/molecules171012187>
26. Gorobets NY, Yousefi BH, Belaj F, Kappe CO (2004) Rapid microwave-assisted solution phase synthesis of substituted 2-pyridone libraries. *Tetrahedron* 60(39):8633–8644. <https://doi.org/10.1016/j.tet.2004.05.100>
27. Dridi KM, Said RB, Arfaoui Y, Al-Ayed AS (2013) Activated bentonite promoted Friedländer condensation reactions: synthesis of thieno [2, 3-b] quinolinones and tacrines analogues derivatives. *Eur J Chem* 4(3):216–219. <https://doi.org/10.5155/eurjchem.4.3.216-219.788>
28. Jabli D, Dridi K, El Efrat ML (2014) A convenient synthesis of new 2-cyanomethylthieno [3,2-e][1,2,4]-triazolo [1,5-c] pyrimidine derivatives. *Lett Org Chem* 11(6):403–408
29. Todde S, Moresco RM, Simonelli P, Baraldi PG, Cacciari B, Spalluto G, Magni F (2000) Design, radiosynthesis, and bio-distribution of a new potent and selective ligand for in vivo imaging of the adenosine A2A receptor system using positron emission tomography. *J Med Chem* 43(23):4359–4362. <https://doi.org/10.1021/jm0009843>
30. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Scalmani G, Barone V, Mennucci B, Petersson GA, Nakatsuji H (2009) Gaussian 09, R.A. Gaussian Inc., Wallingford CT 121, pp 150–166
31. Lee C, Yang W, Parr RG (1988) Development of the Colle–Salvetti correlation-energy formula into a functional of the electron density. *Phys Rev B* 37(2):785–789. <https://doi.org/10.1103/PhysRevB.37.785>
32. Becke AD (1993) Density-functional thermochemistry. III. The role of exact exchange. *J Chem Phys* 98(7):5648–5652. <https://doi.org/10.1063/1.464913>
33. Vural H, Uçar I (2016) A mixed experimental and theoretical study on chelidamate copper(II) complex with 4-methylpyrimidine. *J Coord Chem* 69(20):3010–3020. <https://doi.org/10.1080/00958972.2016.1225042>
34. Azhagiri S, Jayakumar S, Gunasekaran S, Srinivasan S (2014) Molecular structure, Mulliken charge, frontier molecular orbital and first hyperpolarizability analysis on 2-nitroaniline and 4-methoxy-2-nitroaniline using density functional theory. *Spectrochim Acta Part A Mol Biomol Spectrosc* 124:199–202. <https://doi.org/10.1016/j.saa.2013.12.106>
35. Milad R, Essalah K, Abderrabba M (2018) Optoelectronic and conductivity of π -conjugated polymers based on phenylenevinylene, 1,3,4-thiadiazole and thiophene: suitable candidates for n-type organic semiconductors. *J Phys Org Chem* 31(2):e3750. <https://doi.org/10.1002/poc.3750>
36. El Bakri Y, Lai CH, Sebhaoui J, Ben Ali A, Essassi EM, Mague JT (2019) Synthesis, spectroscopic characterization, thermal, XRD crystal structure, the PLATON structural analysis, and theoretical studies of a new 1,2,4-triazolo-[1,5-a]pyrimidines derivatives. *J Mol Struct* 1184:12–24. <https://doi.org/10.1016/j.molstruc.2019.01.071>
37. Jabeen K, Javaid A (2008) Antifungal activity of aqueous and organic solvent extracts of allelopathic trees against *Ascochyta rabiei*. *Allelopathy J* 22:231–238
38. Jabli D, Lahbib K, Dridi K, Efrat M L (2015) Antibacterial Study Novel 2-cyanomethylthieno [3,2-e] [1,2,4]- triazolo[1,5-c]pyrimidine. *J Pharm Chem Biol Sci* 3(2): 178–187
39. Abdel-Megeid FME, Hassan NA, Zahran MA, Rashad AE (1998) Synthesis of 5,6-dihydronaphtho 1',2': 4,5 thieno 2,3-d pyrimidines, 5,6-dihydronaphtho 1',2': 4,5 thieno3,2-e 1,2,4 triazolo 1,5-c pyrimidines, and some of their nucleosides. *Sulfur Lett* 21(6):269–284
40. Chen H, Yan K (2011) 6-Benzyl-2-[(triphenyl- λ 5-phosphanylidene) amino]-4, 5, 6, 7-tetrahydrothieno [2, 3-c] pyridine-3-carbonitrile. *Acta Crystallogr Sect E Struct Rep Online* 67(10):o2548–o2548. <https://doi.org/10.1107/S1600536811035082>
41. Murray PR, Baron EJ, Jorgensen JH, Pfaller MA, Tenover FC, Tenover FC (2003) Manual of clinical microbiology. American Society for Microbiology Press, Washington, DC, p 1212
42. Delost MD (1997) Introduction to diagnostic microbiology: a text and workbook. Louis, Mosby Inc, St, p 552
43. Al-Taisan KM, Al-Hazimi H, Al-Shihry SS (2010) Synthesis, characterization and biological studies of some novel thieno [2, 3-d] pyrimidines. *Molecules* 15(6):3932–3957. <https://doi.org/10.3390/molecules15063932>