3-ALKOXY-1,5-DIARYL-4,5-DIHYDROXYIMIDAZOLIDIN-2-ONES AND 3-ALKOXY-1-ALKYL-5-ARYL-4,5-DIHYDROXYIMIDAZOLIDIN-2-ONES: SYNTHESIS AND STRUCTURE

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It has been found that 4-nitrophenylglyoxal reacts with *N*-alkoxy-*N'*-arylureas and *N*-alkoxy-*N'*-alkylureas in acetic acid medium with the selective formation of the diastereomers of the 3-alkoxy-1,5-diaryl-4,5-dihydroxyimidazolidin-2-ones and 3-alkoxy-1-alkyl-5-aryl-4,5-dihydroxyimidazolidin-2-ones with *cis*-orientation of OH-groups. The X-ray structural analysis of 3-propyloxy-4S,5S-4,5-dihydroxy-1-methyl-5-(4-nitrophenyl)imidazolidin-2-one and of 3-*n*-butyloxy-4S,5S-4,5-dihydroxy-1-(4-methylphenyl)-5-(4-nitrophenyl)imidazolidin-2-one has demonstrated this structural feature of these compounds.

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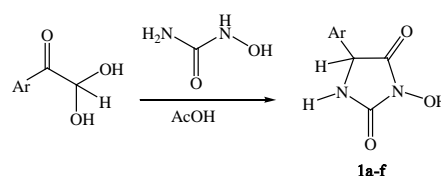   Phone: +380-97-651-61-72
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INTRODUCTION

Arylglyoxals are widely used in syntheses of heterocycles as syntones.[1-6] But the study of the arylglyoxals interaction with *N*-hydroxyurea[7-9] and its derivatives[8,10] has started recently and needs to be continued.

Arylglyoxals such as phenyl-, 4-bromophenyl-, 4-chlorophenyl-, 4-fluorophenyl-, 4-methoxyphenyl- and 4-methylglyoxal easily react with *N*-hydroxyurea in acetic acid medium (Scheme 1) at the room temperature yielding the proper 5-aryl-3-hydroxyimidazolidine-2,4-diones (5-aryl-3-hydroxyhydantoins) **1a-f**.[8] However, 4-nitrophenylglyoxal in acetic acid medium at room temperature reacts with *N*-hydroxyurea giving only a mixture of 5-aryl-3,4,5-trihydroxyimidazolidin-2-ones, **2a** and **3a,** in molar ratio near 3:1 (room temp., 25 h).[9] 3-Hydroxy-5-(4-nitrophenyl)hydantoin (**1g**) is not formed. This example has demonstrated, that the presence of a strong electron-withdrawing substituent on the benzene ring of arylglyoxals prevents a further conversion of 5-aryl-3,4,5-trihydroxyimidazolidin-2-ones into 5-aryl-3-hydroxy-imidazolidin-2,4-diones.[9]

We have obtained similar results in aqueous medium. 4-Nitrophenylglyoxal[9] and 4-chlorophenylglyoxal[7] form only the mixtures of 5-aryl-3,4,5-trihydroxyimidazolidin-2-ones (**2a**,**b** and **3a**,**b**) at 14-20 °C (Scheme 2).

Ar = p-XC$_6$H$_4$, X = H (a), Cl(b), Me(c), OMe(d), Br(e), F(f)

Scheme 1. Arylglyoxal's interaction with *N*-hydroxyurea in acetic acid (Ref. 8).


Ar = p-O$_2$NC$_6$H$_4$ (a); p-ClC$_6$H$_4$(b)
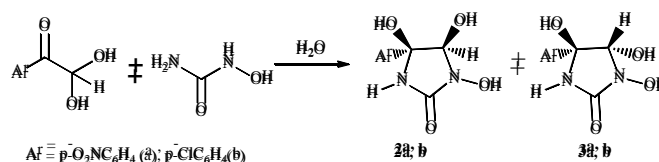
Scheme 2. Interaction of 4-nitrophenylgyoxal hydrate and 4-chlorophenylglyoxal hydrate with *N*-hydroxyurea in aqueous medium.

In these mixtures, the diastereomers of 5-aryl-3,4,5-trihydroxyimidazolidin-2-ones (**2a, 2b**) with *cis* orientation of hydroxyl groups at C-4,5 carbon atoms are the main products.[7-9] The structure of compounds **2a,b** has been proved by XRD study.[7,9]
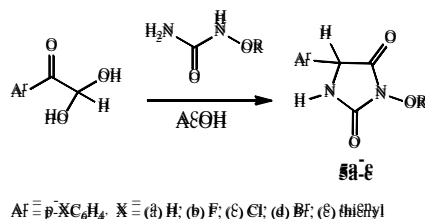
Phenylglyoxal reacts with *N*-hydroxyurea in aqueous solution at the room temperature, forming the mixture of unstable 3,4,5-trihydroxy-5-phenylimidazolidin-2-ones (**2c**,**3c**) and 3-hydroxy-5-phenylhydantoin (**1a**).[7,8] The compounds **2c** and **3c** are easily transformed to hydantoin **1a** by heating.[7,8]

4-Methoxyphenylglyoxal and 4-methylphenylglyoxal form with *N*-hydroxyurea a mixture of 5-aryl-3-hydroxyhydantoins (**1c**,**1d**) and acyclic ureas (**4c**,**4d**)[7] (Scheme 3).
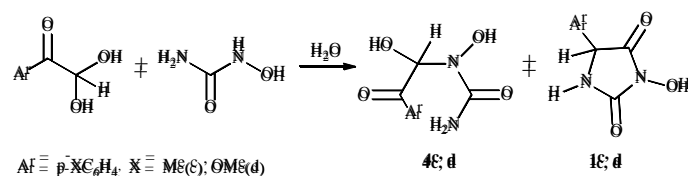
Scheme 3. Interaction of 4-methylphenylgyoxal hydrate and 4-methoxyphenylglyoxal hydrate with *N*-hydroxyurea in aqueous solution.

In acetic acid medium, the majority of arylglyoxals reacts with *N*-alkoxyureas forming only 3-alkoxy-5-arylhydantoins (**5a-e**) (Scheme 4).


Scheme 4. Interaction of arylglyoxals with *N*-alkoxyureas in acetic acid medium.

The arylgyoxal's interaction with *N*-alkoxy-*N'*-arylureas (**6**) has been particularly studied.[10] It has been shown that anhydrous phenylglyoxal reacts with *N*-ethoxy-*N'*-phenylurea (**6a**) in CH₂Cl₂ at 20 ºC yielding 3-ethoxy-1,5-bis(phenyl)imidazolidine-2,4-dione **7** in moderate (46 %) yield[10] (Scheme 5). Using *N*-benzyloxy-*N'*-(4-nitrophenyl)urea (**6b**), anhydrous phenylglyoxal produces (CH₂Cl₂, 20 ºC) 3-benzyloxy-4,5-dihydroxy-1-(4-nitrophenyl)-5-phenylimidazolidine-2-one **8** (56 %) and 3-benzyloxy-1-(4-nitrophenyl)-5-phenylhydantoin **9** (6 %).[10]
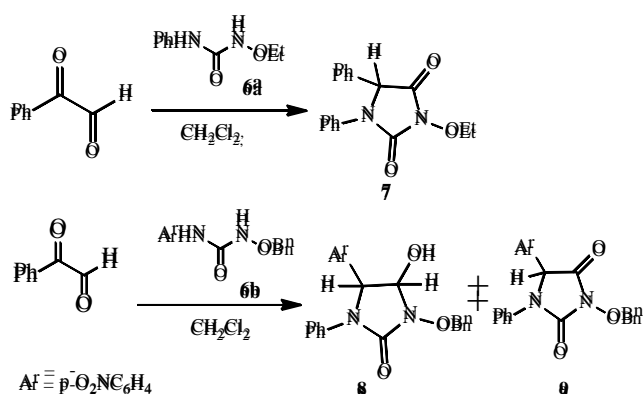
Scheme 5. Interaction of phenylglyoxal with *N*-alkoxy-*N'*-arylureas.
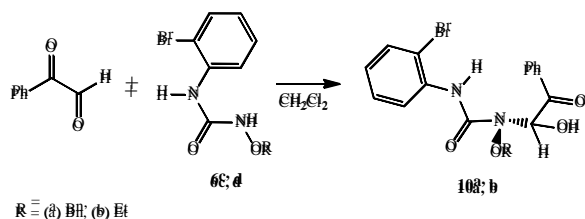
Scheme 6. Synthesis acyclic substituted *N*-alkoxyureas **10**.

But the reaction between phenylglyoxal and *N*-benzyloxy-*N'*-(2-bromophenyl)urea (**6c**) and *N*-ethoxy-*N'*-(2-bromophenyl)urea (**6d**) in dichloromethane solution (Scheme 6) at room temperature gives only acyclic ureas (**10a,b**).[10,11] It is probable that the bulky ortho-bromo substituent prevents the further cyclization. The structure of ureas **10a,b** has been confirmed by XRD study. In the crystalline state, compound **10a** exists in two forms (**10aA** and **10aB**), which are distinguished by the pyramidality degree of the acyclic amide nitrogen atom. The sum of bond angles centered of this atom (Σß) is 336.0(3)º and 341.2(3)º in the molecules **10aA** and **10aB**[10], respectively. The urea **10b** exists in the single form, the sum of bond angles centered on the nitrogen atom is 340.0(3)º.[11]

So, the goal of our current research was to investigate the interaction of 4-nitrophenylglyoxal with *N*-alkoxy-*N'*-arylureas **6** in acetic acid medium.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian VXP-300 spectrometer and Varian Jemini 400 spectrometer (300 and 400 MHz, respectively). ^{13}C NMR spectra were recorded on a Varian VXP-300 spectrometer (75 MHz) and Varian Jemini 400 spectrometer (100 MHz). The solvents were DMSO-d_6 (for the compounds **6**, **11a**-**g**, **13b** and **14a, b**) and CDCl₃ (for the compounds **6a, 13a** and **14a**) ^{1}H NMR chemical shifts were reported relative to the residual solvent protons as an internal standard ((CD₃)₂SO: 2.500 ppm) or with TMS as an internal standard (in CDCl₃). Solvent carbon atoms served as an internal standard for ^{13}C NMR spectra ((CD₃)₂SO: 39.52 ppm). Mass spectra were recorded on a VG 70-70EQ mass spectrometer in fast atom bombardment mode (FAB). The solvents were purified and dried according to the standard procedures. 4-Nitrophenylglyoxal hydrate was obtained according to published procedures.[9]

N-Ethoxy-*N'*-phenylurea (6a)

This compound was obtained according to published procedures,[10] yield was 60 %, colorless crystals, m.p. 101-104 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.213 (3H, t, *J* = 7.2 Hz, NOCH₂Me), 3.823 (2H, q, *J* = 7.2 Hz, NOCH₂Me), 6.985 (1H, t, *J* = 7.6 Hz, C(4)H Ph), 7.257 (2H, t, *J* = 7.6, Hz C(3)H, C(5)H Ph), 7.567 (2H, d, *J* = 7.6 Hz, C(2)H, C(6)H Ph), 8.702 (1H, s, NH), 9.410 (1H, s, NHO). ^{1}H NMR (300 MHz, CDCl₃): δ = 1.337 (3H, t, *J* = 7.0 Hz, NOCH₂Me), 3.987 (2H, q, *J* = 7.0 Hz, NOCH₂Me), 7.105 (1H, t, *J* = 7.8 Hz, C(4)H Ph), 7.336 (2H, t, *J* = 7.8 Hz, C(3)H, C(5)H Ph), 7.488 (2H, d, *J* = 7.8 Hz, C(2)H, C(6)H Ph), 7.608 (1H, s, NH), 7.708 (1H, s, NHO). MS (FAB) m/z 361 [2M+H]⁺ (4), 181 [M+H]⁺(100). Anal. Calc. for C₉H₁₂N₂O₂: C 59.99, H 6.71, N 15.55. Found: C 59.81, H 6.83, N 15.44.

N-Methoxy-*N'*-phenylurea (6e)

A solution of phenyl isocyanate (918 mg, 7.706 mmol) in dry benzene (8 mL) was added to the solution of methoxyamine (444 mg, 9.434 mmol) in dry benzene (4

mL). The reaction mixture was maintained in a closed bulb at 20 ºC for 6 days, the obtained precipitate was then filtered off, washed with dry benzene (1mL) and dried under vacuum (2 mm Hg) to yield **6e** as colorless crystals, m.p. 112–113 ºC. [1]H (400 MHz, DMSO-d_6): δ = 3.615 (3H, s, NOMe), 6.984 (1H, t, *J* = 7.6 Hz, C(4)H Ph), 7.255 (2H, t, *J* = 7.6 Hz, C(3)H, C(5)H Ph), 7.575 (2H, d, , *J* = 7.6 Hz, C(2)H, C(6)H Ph), 8.840 (1H, s, NH), 9.482 (1H, s, NHO). MS (FAB) m/z 333 [2M+H]$^+$ (10), 167 [M+H]$^+$(100). Anal. Calc. for $C_8H_{10}N_2O_2$: C 57.82, H 6.07, N 16.86. Found: C 57.65, H 6.26, N 16.73.

In a similar manner, *N*-alkoxy-*N'*-arylureas (**6f-j**) and *N*-alkoxy-*N'*-alkylureas (**13a**, **b**) were obtained:

N-Benzyloxy-*N'*-phenylurea (6f)

This compound was obtained as colourless crystals, yield 78 %, m.p. 104-105ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.824 (2H, s, NOCH$_2$), 6.981 (1H, t, *J* = 7.6 Hz, C(4)H PhN), 7.252 (2H, t, *J* = 7.6 Hz, C(3)H, C(5)H PhN), 7.331 (1H, t, *J* = 6.8 Hz, C(4)H PhCH$_2$), 7.384 (2H, t, *J* = 6.8 Hz, C(3)H, C(5)H PhCH$_2$), 7.463 (2H, d, *J* = 6.8 Hz, C(2)H, C(6)H PhCH$_2$), 7.514 (2H, d, *J* = 7.6 Hz, C(2)H, C(6)H PhN), 8.704 (1H, s, NH), 9.465 (1H, s, NHO). MS (FAB) m/z 243 [M+H]$^+$(86), 91 Bn$^+$ (100). Anal. Calc. for $C_{14}H_{14}N_2O_2$: C 69.41, H 5.82, N 11.56. Found: C 69.57, H 5.75, N 11.50.

N-Methoxy-*N'*-(4-methylphenyl)urea (6g)

Obtained as colourless crystals, yield 95 %, m.p. 152-154 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) :δ = 2.233 (3H, s, Me), 3.605 (3H, s, NOMe), 7.059 (2H, d, *J* = 8.4 Hz, C(3)H, C(5)H Ar), 7.446 (2H, d, *J* = 8.4 Hz, C(2)H, C(6)H Ar), 8.745 (1H, s, NH), 9.411 (1H, s, NHO). MS (FAB) m/z 181 [M+H]$^+$ (100). Anal. Calc. for $C_9H_{12}N_2O_2$: C 59.99, H 6.71, N 15.55. Found: C 59.68, H 6.56, N 15.39.

N-n-Butyloxy-*N'*-(4-methylphenyl)urea (6h)

Obtained as colourless crystals, yield 72 %, m.p. 78-79 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.900 (3H, t, *J* = 7.2 Hz, NO(CH$_2$)$_3$Me), 1.355 (2H, sex, *J* = 7.2 Hz, NO(CH$_2$)$_2$CH$_2$Me), 1.602 (2H, quint, *J* = 7.2 Hz, NOCH$_2$CH$_2$CH$_2$Me), 2.223 (3H, s, Me), 3.756 (2H, t, *J* = 7.2 Hz, NOCH$_2$CH$_2$CH$_2$Me), 7.061 (2H, d, *J* = 8.4 Hz, C(3)H, C(5)H Ar), 7.426 (2H, d, *J* = 8.4 Hz, C(2)H, C(6)H Ar), 8.551 (1H, s, NH), 9.348 (1H, s, NHO). MS (FAB) m/z 223 [M+H]$^+$ (100), 133 (10), 106 (22). Anal. Calc. for $C_{12}H_{18}N_2O_2$: C 64.84, H 8.16, N 12.60. Found: C 64.79, H 8.21, N 12.43.

N-Ethoxy-*N'*-(4-bromophenyl)urea (6i)

Obtained as colourless crystals, yield 92 %, m.p. 109-110 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.204 (3H, t, *J* = 7.2 Hz, NOCH$_2$Me), 3.812 (2H, q, *J* = 7.2 Hz, NOCH$_2$Me), 7.432 (2H, d, *J* = 9.2 Hz, C(2)H, C(6)H C$_6$H$_4$Br), 7.569 (2H, d, *J* = 9.2 Hz, C(3)H, C(5)H C$_6$H$_4$Br), 8.874 (1H, s, NH), 9.515 (1H, s, NHO). MS (FAB) m/z 261 [M+H]$^+$ (16), 259 [M+H]$^+$ (15), 102 (100). Anal. Calc. for $C_9H_{11}BrN_2O_2$: C 41.72, H 4.28, N 10.81. Found: C 41.59, H 4.21, N 10.56.

N-n-Butyloxy-*N'*-(4-bromophenyl)urea (6j)

Obtained as colourless crystals, yield 61 %, m.p. 104-105 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.89 (3H, t, *J* = 7.4 Hz, NO(CH$_2$)$_3$Me), 1.35 (2H, sex, *J* = 7.4 Hz, NOCH$_2$CH$_2$CH$_2$Me), 1.60 (2H, quint, *J* = 7.4, NOCH$_2$CH$_2$CH$_2$Me), 3.76 (2H, t, *J* = 6.6 Hz, NOCH$_2$), 7.43 (2H, d, *J* = 8.8 Hz, C(2)H,C(6)H, C$_6$H$_4$Br), 7.56 (2H, d, *J* = 8.8 Hz, C(3)H,C(5)H, C$_6$H$_4$Br), 8.85 (1H, s, NH), 9.54 (1H, s, NHO). MS (FAB) m/z 289 [M+H]$^+$ (95), 287 [M+H]$^+$ (100), 273 (17), 271 (17), 209 (40). Anal. Calc. for $C_{11}H_{15}BrN_2O_2$: C 46.01, H 5.26, N 9.76. Found: C 46.13, H 5.34, N 9.58.

N-Propyloxy-*N'*-methylurea (13a)

Obtained as colourless oil, yield 90 %, n_D^{20} 1.4550. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.95 (3H, t, *J* = 7.0 Hz, NOCH$_2$CH$_2$Me), 1.67 (3H, sex, *J* = 7.0 Hz, NOCH$_2$CH$_2$Me), 2.86 (3H, br. s, NMe), 3.77 (2H, t, *J* = 7.0 Hz, NOCH$_2$), 5.73 (1H, s, NH), 7.61 (1H, s, NHO). Anal. Calc. for $C_5H_{12}N_2O_2$: C 45.44, H 9.15, N 21.20. Found: C 45.37, H 9.24, N 21.46.

N-Ethoxy-*N'*-(1-naphthyl)methylurea (13b)

Obtained as colourless crystals, yield 74 %, m.p. 145-146ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.157 (3H, t, *J* = 7.0 Hz, NOCH$_2$Me), 3.752 (2H, q, *J* = 7.0 Hz, NOCH$_2$Me), 4.740 (2H, d, *J* = 6.0 Hz, NCH$_2$), 7.353–7.386 (1H, m, H C$_{10}$H$_7$), 7.414–7.430 (1H, m, H C$_{10}$H$_7$), 7.495 (1H, t, *J* = 6.8 Hz, H C$_{10}$H$_7$), 7.535–7.572 (2H, m, NH and H C$_{10}$H$_7$), 7.827 (1H, d, *J* = 8.0 Hz, H C$_{10}$H$_7$), 7.942 (1H, d, *J* = 8.0 Hz, H C$_{10}$H$_7$), 8.173 (1H, d, *J* = 6.8 Hz, H C$_{10}$H$_7$), 9.138 (1H, s, NHO). MS (FAB) m/z 245 [M+H]$^+$ (52), 243 [M–H]$^+$ (7), 198 (6), 156 (13), 141 NafCH$_2^+$ (100), 117(14). Anal. Cal. for $C_{14}H_{16}N_2O_2$: C 68.83, H 6.60, N 11.47. Found: C 68.73, H 6.51, N 11.38.

Preparation of *cis*-diastereomer, 4*S*,5*S*-dihydroxy-3-methoxy-5-(4-nitrophenyl)-1-phenylimidazolidin-2-one (11a)

4-Nitrophenylglyoxal hydrate (102 mg, 0.518 mmol) was added to the solution of **6e** (86 mg, 0.518 mmol) in acetic acid (5 mL). The reaction mixture was stirred at 19 ºC for 19 h, then it was frozen and acetic acid was evaporated at 15ºC under vacuum (2 mmHg), the residue was washed by cold water (5 mL), dried under vacuum (2 mm Hg) to yield 154 mg (86 %, purity 95 %) *cis*-diastereomer, 4*S*,5*S*-4,5-dihydroxy-3-methoxy-5-(4-nitrophenyl)-1-phenylimidazoli-din-2-one (**11a**) as colourless crystals, m.p. 158-159 (with decomp., CH$_2$Cl$_2$–hexane). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.828 (3H, s, NOMe), 4.931 (1H, d, *J* = 6.5 Hz, CHOH), 7.066 (1H, t, *J* = 8.0 Hz, C(4)H Ph), 7.136 (1H, d, *J* = 6.5 Hz, CHOH), 7.207 (2H, t, *J* = 8.0 Hz, C(3)H, C(5)H Ph), 7.288 (1H, s, OH), 7.384 (2H, d, *J* = 8.0 Hz, C(2)H, C(6)H Ph), 7.763 (2H, d, *J* = 8.5 Hz, C(2)H, C(6)H C$_6$H$_4$NO$_2$), 8.150 (2H, d, *J* = 8.5 Hz, C(3)H, C(5)H C$_6$H$_4$NO$_2$). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 64.0 (OMe), 87.1, 87.6 (CHOH, COH), 123.2, 124.8, 125.4, 128.26, 128.29 (C-2,C-6 C$_6$H$_4$NO$_2$,C-3,C-5 Ph, C-4 Ph, C-3,C-5 C$_6$H$_4$NO$_2$, C-2,C-6 Ph), 135.9 (C-1, C$_6$H$_4$NO$_2$), 147.0, 147.2 (C-1 Ph, C-4 C$_6$H$_4$NO$_2$), 156.7 (C=O). MS (FAB) m/z 346 [M+H]$^+$(100).

MS (FAB, KI) m/z 384 [M+K]$^+$(20), 346 [M+H]$^+$ (82), 192(100). Anal. Calc. for $C_{16}H_{15}N_3O_6$: C 55.65, H 4.38, N 12.17. Found: C 55.63, H 4.39, N 12.10.

3-Ethoxy-4*S*,5*S*-4,5-dihydroxy-5-(4-nitrophenyl)-1-phenylimidazolidin-2-one (11b)

4-Nitrophenylglyoxal hydrate (176 mg, 0.893 mmol) was added to the solution of **6a** (161 mg, 0.893 mmol) in acetic acid (6 mL). The reaction mixture was stirred at 17 ℃ for 23 h, then it was frozen and acetic acid was evaporated at 15℃ under vacuum (2 mmHg), the residue was washed with water (6 mL), dried under vacuum (2 mmHg) to yield 286 mg (89 %, purity 96 %) *cis*-diastereomer, 3-ethoxy-4*S*,5*S*-4,5-dihydroxy-5-(4-nitrophenyl)-1-phenylimidazolidin-2-one (**11b**) as colourless crystals, m.p. 145-146℃ (with decomp., THF–CH$_2$Cl$_2$–C$_6$H$_{14}$). ^{1}H NMR (300 MHz, DMSO-*d*$_6$):δ = 1.24 (3H, t, *J* = 6.9 Hz, NOCH$_2$Me), 4.06 (2H, q, *J* = 6.9 Hz, NOC$\underline{H_2}$Me), 4.91 (1H, d, *J* = 6.6 Hz, C$\underline{H}$OH), 7.06 (1H, t, *J* = 7.5 Hz, C(4)H, Ph), 7.11 (1H, d, *J* = 6.6 Hz, CHO$\underline{H}$), 7.21 (2H, t, *J* = 7.5 Hz, C(3)H, C(5)H Ph), 7.25 (1H, s, OH), 7.40 (2H, d, *J* = 7.5 Hz, C(2)H, C(6)H Ph), 7.77 (2H, d, *J* = 8.7 Hz, C(2)H, C(6)H C$_6$H$_4$NO$_2$), 8.15 (2H, d, *J* = 8.7 Hz, C(3)H, C(5)H C$_6$H$_4$NO$_2$). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 13.97 (Me), 71.36 (NOCH$_2$), 87.14, 87.74 (CHOH, COH), 123.29, 124.72, 125.33, 128.27, 128.31, 136.03 (C Ph, C C$_6$H$_4$NO$_2$), 147.25, 147.26 (C-1 Ph, C-4 C$_6$H$_4$NO$_2$), 156.93 (C=O). MS (FAB) m/z 360 [M+H]$^+$(100), 342 [M+H-H$_2$O]$^+$(8), 223 (74), 181 (99), 150 (26), 91 (30). Anal. Calc. for $C_{17}H_{17}N_3O_6$: C 56.82, H 4.77, N 11.69. Found: C 56.55, H 4.70, N 11.79.

3-Benzyloxy-4*S*,5*S*-4,5-dihydroxy-5-(4-nitrophenyl)-1-phenylimidazolidin-2-one (11c)

4-Nitrophenylglyoxal hydrate (80 mg, 0.406 mmol) was added to the solution of **6f** (98 mg, 0.405 mmol) in acetic acid (5 mL), the reaction mixture was stirred at 18 ℃ for 21 h, then it was frozen and acetic acid was evaporated at 16℃ under vacuum (2 mm Hg), the residue was twice washed with cold water (3 mL), dried under vacuum (2 mm Hg) giving 147 mg (86 %, purity 96 %) 3-benzyloxy-4S,5S-4,5-4,5-dihydroxy-5-(4-nitrophenyl)-1-phenylimidazolidin-2-one (**11c**) as colourless solid, m.p. 62-65℃ (with decomp., CH$_2$Cl$_2$–hexane). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 4.813 (1H, d, *J* = 6.0 Hz, C$\underline{H}$OH), 5.053 (2H, s, NOCH$_2$), 7.068 (1H, t, *J* = 7.6 Hz, C(4)H PhN), 7.212 (2H, t, *J* = 7.6 Hz, C(3)H, C(5)H PhN), 7.272 (1H, d, *J* = 6.0 Hz, CHO$\underline{H}$), 2.277 (1H, s, OH), 7.313–7.414 (5H, m, CH$_2$$\underline{Ph}$), 7.481 (2H, d, *J* = 6.8 Hz, C(2)H, C(6)H PhN), 7.704 (2H, d, *J* = 8.8 Hz, C(2)H, C(6)H C$_6$H$_4$NO$_2$), 8.136 (2H, d, *J* = 8.8 Hz, C(3)H, C(5)H C$_6$H$_4$NO$_2$). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 77.86 (NOCH$_2$), 87.28, 87.44 (CHOH, COH), 123.30, 124.71, 125.37, 128.12, 128.20, 128.28, 128.35, 129.06, (C PhN, C P$\underline{h}$CH$_2$, C C$_6$H$_4$NO$_2$), 135.93, 136.08 (C-1 Bn, C-1 C$_6$H$_4$NO$_2$), 147.18, 147.29 (C-1 PhN, C-4 C$_6$H$_4$NO$_2$), 156.77 (C=O). MS (FAB) m/z 422 [M+H]$^+$(16), 243 (34), 194 (7), 150 (15), 91 Bn$^+$ (100). Anal. Calc. for $C_{22}H_{19}N_3O_6$ C 62.70, H 4.54, N 9.97. Found: C 62.39, H 4.65, N 9.81.

4*S*,5*S*-4,5-Dihydroxy-3-methoxy-1-(4-methylphenyl)-5-(4-nitrophenyl)imidazolidin-2-one (11d)

4-Nitrophenylglyoxal hydrate (151 mg, 0.765 mmol) was added to the solution of **6g** (138 mg, 0.765 mmol) in acetic acid (5 mL). The reaction mixture was stirred at 17 ℃ for 21 h, then it was frozen and acetic acid was evaporated at 16 ℃ under vacuum (2 mm Hg), the residue was twice washed with cold water (5 mL), dried under vacuum (2 mm Hg) giving 245 mg (89 %, purity 95 %) **11d** as colourless crystals, m.p. 157-159℃ (with decomp., CH$_2$Cl$_2$–hexane). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 2.168 (3H, s, Me), 3.825 (3H, s, NOMe), 4.924 (2H, d, *J* = 6.4 Hz, C$\underline{H}$OH), 7.005 (2H, d, *J* = 7.6 Hz, C(3)H, C(5)H C$_6$$\underline{H_4}$Me), 7.099 (1H, d, *J* = 6.4 Hz, CHO$\underline{H}$), 7.237 (1H, s, COH), 7.248 (2H, d, *J* = 7.6 Hz, C(2)H, C(6)H C$_6$$\underline{H_4}$Me), 7.753 (2H, d, *J* = 8.4 Hz, C(3)H, C(5)H C$_6$H$_4$NO$_2$), 8.142 (2H, d, *J* = 8.4 Hz, C(2)H, C(6)H C$_6$H$_4$NO$_2$). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 20.43 (Me), 64.05 (NOMe), 87.13, 87.74 (CHOH, COH), 123.25, 125.23, 128.39, 128.86, 133.24, 134.90 (C Ar), 147.18, 147.28 (C-1 C$_6$H$_4$Me, C-4 C$_6$H$_4$NO$_2$), 156.92 (C=O). MS (FAB) m/z 360 [M+H]$^+$(86), 342 [M+H-H$_2$O]$^+$(8), 299 (28), 257 (10), 209 (100), 181 (85), 150 (40), 133 (44), 106 (25), 90 (39). Anal. Calc. for $C_{17}H_{17}N_3O_6$: C 56.82, H 4.77, N 11.69. Found: C 56.85, H 4.77, N 11.46.

3-*n*-Butyloxy-4*S*,5*S*-4,5-dihydroxy-1-(4-methylphenyl)-5-(4-nitrophenyl)imidazolidin-2-one (11e)

4-Nitrophenylglyoxal hydrate (105 mg, 0.533 mmol) was added to the solution of **6h** (119 mg, 0.533 mmol) in acetic acid (4 mL). The reaction mixture was stirred at 17 ℃ for 19 h, then it was frozen and acetic acid was evaporated under vacuum (2 mm Hg), the residue was twice washed with cold water (4 mL) at 4 ℃ for 20 h, dried under vacuum (2 mmHg) giving 193 mg (90 %, purity 94 %) **11e** as colourless crystals, m.p. 139-141 (with decomposition, CH$_2$Cl$_2$-hexane).

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ = 0.902 (3H, t, *J* = 7.2 Hz, NOCH$_2$CH$_2$CH$_2$$\underline{Me}$), 1.385 (2H, sex, *J* = 7.2 Hz, NOCH$_2$CH$_2$$\underline{CH_2}$Me), 1.617 (2H, quint, *J* = 7.2 Hz, NOCH$_2$$\underline{CH_2}CH_2$Me), 2.166 (3H, s, Me), 3.948–4.046 (2H, m, NOCH$_2$), 4.893 (1H, d, *J* = 6.0 Hz, C$\underline{H}$OH), 7.000 (2H, d, *J* = 8.4 Hz, C(3)H, C(5)H C$_6$H$_4$Me), 7.029 (1H, d, *J* = 6.0 Hz, CHO$\underline{H}$), 7.191 (1H, s, OH), 7.255 (2H, d, *J* = 8.4 Hz, C(2)H, C(6)H C$_6$H$_4$Me), 7.755 (2H, d, *J* = 8.1 Hz, C(2)H, C(6)H C$_6$H$_4$NO$_2$), 8.141 (2H, d, *J* = 8.1 Hz, C(3)H, C(5)H C$_6$H$_4$NO$_2$). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 13.78 [(CH$_2$)$_3$$\underline{Me}$], 18.60 (CH$_2$), 20.39 (C$_6H_4$$\underline{Me}$), 30.08 (CH$_2$), 75.66 (NOCH$_2$), 87.08, 87.94 (CHOH, COH), 123.21, 125.06, 128.33, 128.80 (C-3, C-5 C$_6$H$_4$NO$_2$, C-3,C-5 C$_6$H$_4$Me, C-2,C-6 C$_6$H$_4$Me, C-2, C-6 C$_6$H$_4$NO$_2$), 133.33, 134.71 (C-4 C$_6$H$_4$Me, C-1 C$_6$H$_4$NO$_2$), 147.24, 147.30 (C-1 C$_6$H$_4$Me, C-4 C$_6$H$_4$NO$_2$), 157.00 (C=O). MS (FAB) m/z 402 [M+H]$^+$(12), 384 [M+H-H$_2$O]$^+$(4), 257 (7), 251 (26), 241 (17), 235 (7), 223 (100), 195 (15), 150 (38), 133 (34), 106 (46). Anal. Calc. for $C_{20}H_{23}N_3O_6$: C 59.84, H 5.78, N 10.47. Found: C 59.73, H 5.86, N 10.39.

1-(4-Bromophenyl)-3-ethoxy-4*S*,5*S*-4,5-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-one (11f)

4-Nitrophenylglyoxal hydrate (56 mg, 0.281 mmol) was added to the solution of **6i** (73 mg, 0.281 mmol) in acetic acid (4 mL). The reaction mixture was stirred at 17 ºC for 22 h, then it was frozen and acetic acid was evaporated at 15ºC under vacuum (2 mm Hg), the residue was twice washed with cold water (5 mL) and dried under vacuum (2 mm Hg) to yield 110 mg (89 %, purity 93 %) of **11f** as colourless crystals, m.p. 165-166ºC (with decomp.)(CH$_2$Cl$_2$-hexane). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.23 (3H, t, *J* = 6.8 Hz, NOCH$_2$Me), 4.05 (2H, q, *J* = 6.8 Hz, NO<u>CH$_2$</u>Me), 4.90 (1H, d, *J* = 6.6 Hz, <u>CH</u>OH), 7.16 (1H, d, *J* = 6.6 Hz, CHO<u>H</u>), 7.35 (1H, s, OH), 7.35–7.43 (4H, m, C$_6$H$_4$Br), 7.76 (2H, d, *J* = 8.7 Hz, C(2)H, C(6)H C$_6$H$_4$NO$_2$), 8.16 (2H, d, *J* = 8.7 Hz, C(3)H, C(5)H C$_6$H$_4$NO$_2$). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 13.94 (Me), 71.40 (NOCH$_2$), 87.13, 87.51 (CHOH, COH), 117.65, 123.39, 126.12, 128.20, 131.25, 135.49 (C Ar), 146.88, 147.35 (C-1 C$_6$H$_4$Br, C-4 C$_6$H$_4$NO$_2$), 156.55 (C=O). MS (FAB) m/z 440 [M+H]$^+$(39), 438 [M+H]$^+$(39), 261(100): 259 (94), 223 (81), 214 (48), 150 (45). Anal. Calc. for C$_{17}$H$_{16}$BrN$_3$O$_6$: C 46.59, H 3.68, N 9.59. Found: C 46.32, H 3.74, N 9.35.

1-(4-Bromophenyl)-3-*n*-butyloxy-4*S*,5*S*-4,5-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-one (11g)

4-Nitrophenylglyoxal hydrate (50 mg, 0.254 mmol) was added to the solution of **6j** (73 mg, 0.254 mmol) in acetic acid (5 mL). The reaction mixture was stirred at 18 ºC for 18 h, then it was frozen and acetic acid was evaporated at 16ºC under vacuum (2 mm Hg), the residue was twice washed with cold water (5 mL) and dried under vacuum (2 mm Hg) to yield 110 mg (93 %, purity 93 %) of **11g** as colourless solid, m.p. 114-117 ºC (with decomp., CH$_2$Cl$_2$-hexane). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.90 (3H, t, *J* = 7.0 Hz, NO(CH$_2$)<u>Me</u>), 1.40 (2H, sex, *J* = 7.0 Hz, NOCH$_2$<u>CH$_2$</u>Me), 1.61 (2H, quint, *J* = 7.0 Hz, NOCH$_2$<u>CH$_2$</u>CH$_2$Me), 3.97–4.02 (2H, m, NO<u>CH$_2$</u>), 4.90 (1H, d, *J* = 6.3 Hz, <u>CH</u>OH), 7.16 (1H, d, *J* = 6.3 Hz, CHO<u>H</u>), 7.33–7.47 (5H, m, C$_6$H$_4$Br and COH), 7.76 (2H, d, *J* = 8.4 Hz, C(2)H, C(6)H C$_6$H$_4$NO$_2$), 8.17 (2H, d, *J* = 8.4 Hz, C(3)H, C(5)H C$_6$H$_4$NO$_2$). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 13.78 [(CH$_2$)$_3$<u>Me</u>], 18.58 (CH$_2$), 30.04 (CH$_2$), 75.72 (NOCH$_2$), 87.12, 87.59 (CHOH, COH), 117.69 (C-4 C$_6$H$_4$Br), 123.40 (C-3, C-5 C$_6$H$_4$NO$_2$), 126.18, 128.24 (C-2,C-6 C$_6$H$_4$NO$_2$, C-2,C-6 C$_6$H$_4$Br), 131.26 (C-3,C-5 C$_6$H$_4$Br), 135.50 (C-1 C$_6$H$_4$NO$_2$), 146.89, 147.38 (C-1 C$_6$H$_4$Br, C-4 C$_6$H$_4$NO$_2$), 156.59 (C=O). MS (FAB) m/z 468 [M+H]$^+$ (19), 466 [M+H]$^+$ (18), 450 [M+H-H$_2$O]$^+$ (10), 289 (100), 287 (84), 251 (88), 195 (68), 150 (94). Anal. Calc. for C$_{19}$H$_{20}$BrN$_3$O$_6$: C 48.94, H 4.32, N 9.01. Found: C 48.75, H 4.46, N 8.96.

4*S*,5*S*-4,5-Dihydroxy-1-methyl-5-(4-nitrophenyl)-3-propyloxyimidazolidin-2-one (14a)

A solution of **13a** (177 mg, 1.336 mmol) in acetic acid (4 mL) was added to the mixture of nitrophenylglyoxal hydrate (263 mg, 1.336 mmol) and acetic acid (2 mL). The reaction mixture was stirred at 11 ºC for 4 h, then it was frozen and acetic acid was evaporated at 11ºC under vacuum (2 mm Hg), the residue was dissolved in water (3 mL) at 4ºC and

the aqueous solution was frozen and acetic acid was evaporated at 10ºC under vacuum (2 mm Hg) to give 400 mg (96 %, purity 99 %) of **14a** as colourless crystals, m.p. 151-152ºC (with decomp., CH$_2$Cl$_2$-hexane). ^{1}H NMR (300 MHz, DMSO-d_6), δ = 0.92 (3H, t, *J* = 7.2 Hz, NOCH$_2$CH$_2$<u>Me</u>), 1.62 (2H, sex, *J* = 7.2 Hz, NOCH$_2$<u>CH$_2$</u>Me), 2.52–2.74 (3H, m, NMe), 3.84–3.96 (2H, m, NOCH$_2$), 4.71 (1H, d, *J* = 7.8 Hz, <u>CH</u>OH), 6.73 (1H, d, *J* = 7.8 Hz, CHO<u>H</u>), 6.78 (1H, s, OH), 7.72 (2H, d, *J* = 8.7 Hz, C(2)H, C(6)H C$_6$H$_4$NO$_2$), 8.28 (2H, d, *J* = 8.7 Hz, C(3)H, C(5)H C$_6$H$_4$NO$_2$). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.95 (3H, t, *J* = 7.2 Hz, NOCH$_2$CH$_2$<u>Me</u>), 1.69 (2H, sex, *J* = 7.2 Hz, NOCH$_2$<u>CH$_2$</u>Me), 2.69 (3H, s, NMe), 3.97 (2H, td, ^{3}*J* = 6.9 Hz, ^{2}*J* = 1.8 Hz, NOCH$_2$), 4.50 (1H, br. s, <u>CH</u>OH), 4.61 (1H, br. s, CHO<u>H</u>), 4.92 (1H, s, OH), 7.66 (2H, d, *J* = 9.0 Hz, C(2)H, C(6)H C$_6$H$_4$NO$_2$), 8.27 (2H, d, *J* = 9.0 Hz, C(3)H, C(5)H C$_6$H$_4$NO$_2$). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 10.30 (Me), 21.23 (OCH$_2$<u>CH$_2$</u>Me), 25.15 (NMe), 77.44 (NOCH$_2$), 85.85, 88.25 (CHOH, COH), 123.39 (C-3,C-5 C$_6$H$_4$NO$_2$), 128.07 123.39 (C-2,C-6 C$_6$H$_4$NO$_2$), 147.12, 147.47 (C-1, C-4 C$_6$H$_4$NO$_2$), 158.79 (C=O). MS (FAB) m/z 312 [M+H]$^+$(69), 294 [M+H–H$_2$O]$^+$(20), 278 (5), 237 (100), 221 (15), 195 (32), 150 (62), 133 (58). Anal. Calc. for C$_{13}$H$_{17}$N$_3$O$_6$: C 50.16, H 5.50, N 13.50. Found: C 50.08, H 5.67, N 13.46.

3-Ethoxy-*4S*,5*S*-4,5-dihydroxy)-1-(1-naphthyl)methyl-5-(4-nitrophenyl)imidazolidin-2-one (14b)

A mixture of 4-nitrophenylglyoxal hydrate (134 mg, 0.680 mmol) and **13b** (157 mg, 0.641 mmol) was dissolved in acetic acid (4 mL) with stirring. The reaction mixture was maintained at 16 ºC for 6 h, then acetic acid was evaporated at 16ºC under vacuum (2 mm Hg), the residue was washed by cold water (5 mL), then it was filtered off and dried under vacuum (2 mm Hg) yielding 252 mg (93 %, purity 93 %) of **14b** as yellowish solid, m.p. 155-156ºC (with decomp., CH$_2$Cl$_2$-hexane). ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 1.254 (3H, t, *J* = 6.8 Hz, NOCH$_2$<u>Me</u>), 3.98–4.13 (2H, m, NO<u>CH$_2$</u>Me), 4.531 (1H, d, ^{2}*J* = 15.0 Hz, NCH$_2$), 4.837 (1H, d, *J* = 6.9 Hz, <u>CH</u>OH), 4.918 (1H, d, ^{2}*J* = 15.0, NCH$_2$), 6.894–6.916 (2H, M, CHO<u>H</u>, COH), 7.09–7.17 (2H, m, C$_{10}$H$_7$), 7.321 (2H, d, *J* = 8.7 Hz, C(2)H, C(6)H C$_6$H$_4$NO$_2$), 7.43–7.52 (3H, m, C$_{10}$H$_7$), 7.672 (2H, d, *J* = 8.7 Hz, C(3)H, C(5)H C$_6$H$_4$NO$_2$), 7.75–7.85 (2H, m, C$_{10}$H$_7$),), 8.07–8.13 (1H, m, C$_{10}$H$_7$). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 14.00 (NOCH$_2$<u>Me</u>), 41.29 (NCH$_2$), 71.38 (NOCH$_2$), 86.02, 87.82 (CHOH, COH), 122.05 (C-3, C-5 C$_6$H$_4$NO$_2$), 123.37, 124.80, 125.55, 126.10, 127.49, 127.50 (C$_{10}$H$_7$), 127.63 (C-2, C-6 C$_6$H$_4$NO$_2$), 128.26, 130.87, 132.53, 132.91 (C$_{10}$H$_7$), 146.63 (C-1 C$_6$H$_4$NO$_2$), 147.14 (C4 C$_6$H$_4$NO$_2$), 158.80 (C=O). MS (FAB) m/z 424 [M+H]$^+$ (15), 245(18), 223(29), 182(28), 156(20), 141 NafCH$_2$$^+$ (100). Anal. Calc. for C$_{22}$H$_{21}$N$_3$O$_6$: C 62.41, H 5.00, N 9.92. Found: C 62.28, H 4.86, N 9.83.

Crystals of the compound **11e** were grown from CH$_2$Cl$_2$-C$_6$H$_{14}$ at 10 °C. The studied crystal was monoclinic, C$_{20}$H$_{23}$N$_3$O$_6$, at 20° C, *a* = 15.261(3) Å, *b* = 19.409(2) Å, *c* = 15.676(3) Å, *β* = 117.31(2) °, *V* = 4125.6(14) Å^3, *M*$_r$ = 401.41, *Z* = 8, space group P2$_1$/c, *d*$_{calc.}$= 1.293 g/cm^3, μ (MoK$_α$) = 0.097 mm $^{-1}$, F(000) = 1696. Crystals of the compound **14a** were grown from CH$_2$Cl$_2$-C$_6$H$_{14}$ at -14 °C. The studied crystal was monoclinic, C$_{13}$H$_{17}$N$_3$O$_6$, at 20 °C, *a* = 25.112(5) Å, *b* = 11.250(2) Å, *c* = 10.591(2) Å, *β* = 94.360(17)°, *V* = 2983.6(11) Å^3, *M*$_r$ = 311.29, *Z* = 8, space group P2$_1$/c, *d*$_{calc.}$= 1.386 g/cm^3, μ(MoK$_α$) = 0.111 mm $^{-1}$,

$F(000) = 1312$. X-ray structural study of compounds **11e** and **14a** was performed on a Xcalibur 3 automatic four-circle diffractometer (MoK$_\alpha$-radiation, graphite monochromator, Sapphire-3 CCD detector, ω-scanning, $2\theta_{max}=50°$).

The structures were solved by direct methods using the SHELX-2016[13] software. The positions of the hydrogen atoms were located from electron density difference maps and refined by the "riding" model with $U_{iso} = nU_{eq}$ of the carrier atoms ($n=1.5$ for methyl groups and hydroxyl groups and $n=1.2$ for other hydrogen atoms). Full-matrix least-squares refinement of the structures against F^2 in anisotropic approximation for non-hydrogen atoms was converged to $wR_2 = 0.230$ using 7224 reflections ($R_1 = 0.1037$ for 2769 reflections with F>4σ(F), S = 0.981) for structure **11e** and $wR_2 = 0.292$ using 1759 reflections ($R_1 = 0.1256$ for 635 reflections with F>4σ(F), S = 0.958) for structure **14a**. The atomic coordinates, molecular geometry parameters, and crystallographic data of compounds **11e** and **14a** were deposited at the Cambridge Crystallographic Data Center, 12 Union Road, CB2, 1EZ UK [fax:+44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk and is available on request quoting the deposit number CCDC 1942124 (**11e**) and number CCDC 1942123 (**14a**)].

RESULTS AND DISCUSSION

We have found that 4-nitrophenylglyoxal with *N*-alkoxy-*N'*-arylureas (**6a,e-j**) in acetic acid medium at 17–20°C selectively forms 3-alkoxy-1-aryl-4,5-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-ones (**11a-g**), mainly as diastereomers with *cis* orientation of 4-HO- and 5-HO-groups (93–96%) (Scheme 7). The diastereomers **12a-g** with *trans* orientation of 4-HO- and 5-HO-groups have been observed in the trace amounts in the reaction mixtures (¹H NMR).
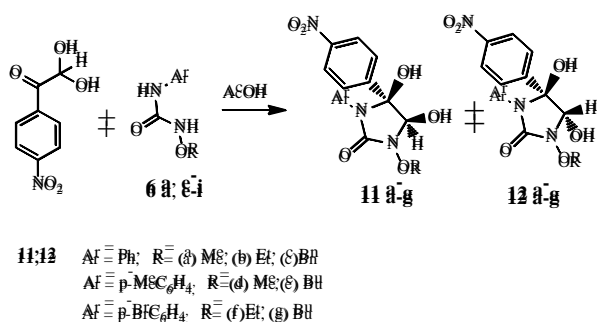
Scheme 7. Synthesis of 3-alkoxy-1-aryl-4,5-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-ones (**11a-g, 12a-g**).

Under similar conditions, 4-nitrophenylglyoxal reacts with *N*-propyloxy-*N'*-methylurea (**13a**) and *N*-ethoxy-*N'*-(1-naphthyl)methylurea (**13b**) give 3-alkoxy-1-alkyl-4,5-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-ones (**14a,b**) mainly as *cis* diastereomer (Scheme 8).

The *trans* diastereomers **15a,b** have been observed in reaction products in the trace amounts as well. The *cis* diastereomers **11** and **14** can be easily obtained in pure form by the crystallization.
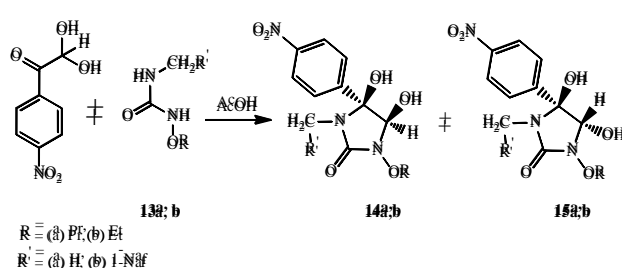
Scheme 8. Synthesis of 3-alkoxy-1-alkyl-4,5-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-ones (**14a,b**, **15a,b**).

Firstly, the *cis* orientation of 4-HO- and 5-HO-groups has been proposed for the compounds **11a-j** and **14a,b** based on their ¹H NMR spectra. For compounds **11a-j** and **14a,b** the doublet of **CH**OH proton is situated in the higher field than doublet of **CH**OH proton of *trans* diastereomers **12a-j** and **15a,b**, as earlier it has been demonstrated for 5-aryl-3,4,5-trihydroxyimidazolidin-2-ones **2a,b**[7-9] (Table 1).

Table 1. The characteristic ¹H NMR chemical shifts of doublet of **CH**OH proton of **2a,b**, **3a,b**, **11a–g**, **12a-g** and **14a,b**, **15a,b**.

cis Diastereomers		*trans* Diastereomers	
	δ, ppm (J, Hz)		δ, ppm (J, Hz)
2a	4.55(7.5)[9]	**3a**	4.91(5.4)[9]
2b	4.52(7.2)[7]	**3b**	4.84(5.7)[8]
11a	4.93(6.5)	**12a**	5.20(5.5)
11b	4.91(6.6)	**12b**	5.18(6.0)
11c	4.81(6.0)	**12c**	5.23(6.0)
11d	4.92(6.4)	**12d**	5.19(4.8)
11e	4.90(6.0)	**12e**	5.17(3.9)
11f	4.90(6.8)	**12f**	5.17(5.7)
11g	4.90(6.3)	**12g**	5.16(5.1)
14a	4.71(7.8)	**15a**	5.04(6.0)
14b	4.81(7.2)	**15b**	5.16(6.0)
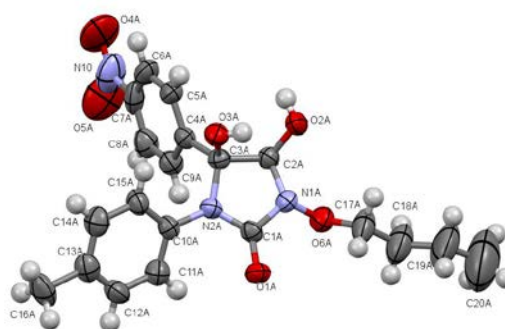
Figure 1. The molecular structure of 3-*n*-butyloxy-4*S*,5*S*-4,5-dihydroxy-1-(4-methylphenyl)-5-(4-nitrophenyl)-imidazolidin-2-one (**11eA**), showing the atom labelling. Displacement ellipsoids are drawn with the 50% probability level according to the data X-ray structural analysis.

There are two molecules of compound **11e** (**11eA** and **11eB**) in the asymmetric part of the unit cell. Molecules **11eA** and **11eB** have some different structural parameters. Earlier the similar existence of compound in the two geometrical forms in the crystal was found for the *N*-alkoxyurea **10a**[10] and in other cases.[13-15]

The five-membered ring has an envelope conformation in both molecules. The C(2) atom deviates on 0.37 Å (**11eA**) and 0.53 Å (**11eB**) off the plain of remaining ring atoms. The N(1) atom has a pyramidal configuration. The sum of bond angles centered at the N(1) atom (Σß) is 339.3° in molecule **11eA** and 336.8 in molecule **11eB**. The N(2) nitrogen atom has a planar configuration (Σß is 358.3° in molecule **11eA** and 359.5° in molecule **11eB**). The C(3)–OH group has axial orientation relative to five-membered ring(the torsion angle N(1)–C(2)–C(3)–O(3) is 97.0(5)° (molecule **11eA**), -87.9(6)° (molecule **11eB**). The C(2)–OH group has equatorial orientation to five-membered ring (the torsion angle C(1)–N(1)–C(2)–O(2) is 143.7(5)° (molecule **11eA**), 154.6(5)° (molecule **11eB**).

The 4-nitrophenyl substituent has equatorial orientation to five-membered ring [the torsion angle N(1)–C(2)–C(3)–C(4) is -142.0(5)°(molecule **11eA**), 152.3(5)°(molecule **11eB**)]. It is rotated relatively to the C(2)–C(3) endocyclic bond [the torsion angle C(2)–C(3)–C(4)–C(9) is 75.8°(molecule **11eA**), 104.4° (molecule **11eB**)]. The nitro group is slightly rotated towards the plane of the aromatic cycle [the torsion angle C(6)–C(7)–N(3)–O(4) is -7.2(2)° (molecule **11eA**), -15.4(2)° (molecule **11eB**), the torsion angle C(8)–C(7)–N(3)–O(5) is -0.3(1)° (molecule **11eA**), -18.6(9)° (molecule **11eB**)].

In the compound **11e** the ordinary bonds O(2)–C(2) and O(3)–C(3) are in some way different: the O(3)–C(3) bond [1.399(6) Å (**11eA**), 1.405(6) Å (**11eB**)] is little bit longer than the O(2)–C(2) bond [1.380(7) Å (**11eA**), 1.369(7) Å (**11eB**)]. The similar bond difference was found for 5-aryl-3,4,5-trihydroxyimidazolidin-2-ones **2a**[9], **2b**[7]. The lengths of O(6)–N(1) bond [1.410(6) Å (**11eA**), 1.401(6) Å (**11eB**)] is similar to the same bond's lengths in compounds **2a,b** [1.398(7) Å in compound **2a**,[9] 1.405(1) Å in compound **2b**[7]].

The butyloxy group has +*ac*-conformation to the endocyclic C(2)–N(1) bond in the molecule **11eA** and –*ac*-conformation in the molecule **11eB** [the torsion angle C(2)-N(1)–O(6)–C(17) is 121.3(6)° (molecule **11eA**), -107.6(6)° (molecule **11eB**)]. It has transoid conformation [the torsion angle N(1)–O(6)–C(17)–C(18) is -179.0(7)° (molecule **11eA**), 170.1(6)° (molecule **11eB**), the torsion angle O(6)–C(17)–C(18)–C(19) is 171.7(1)° (molecule **11eA**), -159.4(1)° (molecule **11eB**)].

In the crystal, the molecules **11eA** and **11eB** are linked into dimers by the intermolecular hydrogen bond O(3B)-H(3B)…O(1A)' (x, y, z) (H…O 1.87 Å, O-H…O 167°). These dimers form the chains toward crystallographic direction [0 0 1] due to intermolecular hydrogen bonds O(3A)–H(3A)…O(2A)' (1-x, 1-y, -z) (H…O 2.23 Å, O–H…O 148°) и O(3B)–H(3B)…O(1A)' (x, y, z) (H…O1.87 Å, O–H…O 167°).

The molecular structure 4*S*,5*S*-4,5-dihydroxy-1-methyl-5-(4-nitrophenyl)-3-propyloxyimidazolidin-2-one (**14a**) is very similar to the molecular structure of compound **11e**.

There are two molecules of 4*S*,5*S*-4,5-dihydroxy-1-methyl-5-(4-nitrophenyl)-3-propyloxyimidazolidin-2-one (**14a**) (**14aA** and **14aB**) in the asymmetric part of the unit cell. These molecules have different structural parameters.
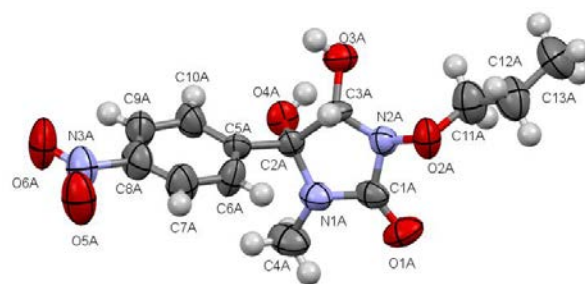

Figure 2. Molecular structure of 4*S*,5*S*-4,5-dihydroxy-1-methyl-5-(4-nitrophenyl)-3-propyloxyimidazolidin-2-one (**14aA**) with atoms represented by thermal vibration ellipsoids of 50% probability level according to the data of X-ray structural analysis.

The five-membered ring has an envelope conformation in both molecules. The C(3) atom deviation of the plane of the remaining ring atoms is 0.42 Å in the molecule 1**4aA** and 0.46 Å in the molecule **14aB**. The nitrogen atom N(1) has the planar configuration (Σβ=356° in the molecule **14aA** and Σβ=357° in the molecule **14aB**). The nitrogen atom N(2) has the pyramidal configuration (Σβ=337.4° in the molecule **14aA** and Σβ=336° in the molecule **14aB**). The hydroxyl group at the C(2) atom has an axial orientation relatively to the five-membered ring [the N(2)–C(3)–C(2)–O(4) torsion angle is -90.6(7)° in **14aA**, 92.3(7)° in **14aB**]. The hydroxyl group at the C3 atom has an equatorial orientation to the five-membered ring (the C(1)–N(2)–C(3)–O(3) torsion angle is -146.2(7)° (**14aA**), 152.1(7)° (**14aB**)).

The 4-nitrophenyl substituent is equatorially oriented to the five-membered ring [the torsion angle N(2)–C(3)–C(2)–C(5) is 147.6(6)° (**14aA**), -150.6(7)° (**11eB**)]. It is rotated towards the C(2)–C(3) endocyclic bond (the torsion angle C(3)–C(2)–C(5)–C(6) is -68.6° (**14aA**), 74.4° (**14aB**)]. The nitro group is slightly rotated towards the plane of the aromatic cycle [the torsion angle C(7)–C(8)–N(3)–O(5) is -2.8(2)° (**14aA**), 10.5(2)° (**14aB**), the torsion angle C(9)–C(8)–N(3)–O(6) is -4.9(2)° (**14aA**), 5.4(1)° (**14aB**)].

In the compound **14a** the ordinary bonds O(4)–C(2) and O(3)–C(3) are in some way different: the O(4)–C(2) bond [1.427(8) Å (**14aA**), 1.431(9) Å(**14aB**)] is a longer than the O(3)–C(3) bond [1.381(9) Å (**14aA**), 1.387(9) Å(**14aB**)]. The similar bond difference takes place in the compounds **2a**,**2b**,**11e**.[7,9] The length of O(2)–N(2) bond [1.420 (8) Å (**14aA**), 1.418 (8) Å (**14aB**)] is similar to the same bond's length in the compound **11e**. The propyloxy group has –*ac*-conformation to the endocyclic C(3)–N(2) bond in the molecule **14aA** and +*ac*-conformation in the molecule **14aB** [the torsion angle C(3)–N(2)–O(2)–C(11) is - 106.8(8)° (**14aA**), 115.5(8) (**14aB**)]. It has transoid conformation [the torsion angle N(2)–O(2)–C(11)–C(12) is 175.8(8)° (**14aA**), 175.5(9)° (**14aB**), the torsion angle O(2)–C(11)–C(12)–C(13) is -174.2(9)° (**14aA**), -179.0(1)° (**14aB**)].

In the crystal molecules **14aA** and **14aB** are linked in the dimers by the intermolecular hydrogen bond O(3B)–H(3B)…O(1A)' (x, y, z) (H…O 1.98 Å, O–H…O 167°). These dimers form the chains toward crystallographic direction [0 1 0] due to intermolecular hydrogen bonds O(3A)–H(3A)…O(4B)' (x,1+y,z) (H…O 2.06 Å, O–H…O 178°) and O(4A)–H(4A)…O(2A)' (x, 1.5-y, -0.5+z) (H…O 2.12 Å, O–H…O 136°) (Figure 3).
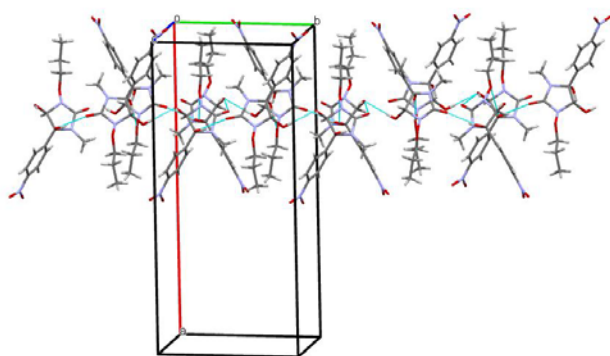
For the studied reaction of arylglyoxals with *N*-hydroxyurea,[7-9] *N*-alkoxy-*N'*-arylureas[10] and *N*-alkoxy-*N'*-alkylureas a possible mechanism results dominating the formation of the diastereomers with *cis* orientation of 4-HO- and 5-HO-groups has been proposed (Scheme 9). At the first stage, the open-chain *N*-alkoxyurea **16A** is formed which has intramolecular hydrogen bond. The intermediate **16A** can isomerize into the enolic form **16B** possessing the same intramolecular hydrogen bond. In the further cyclization of intermediate **16A** (route **i** Scheme 9), or intermediate **16B** (rout **ii** Scheme 9) yields the diastereomer with *cis* orientation of 4-HO- and 5-HO-groups due to presence of this intramolecular hydrogen bond. The mild conditions of the reaction (no heating) preserve the further isomerization of the forming *cis* diastereomers **11**, **14** into *trans* diastereomers **12**, **15**.
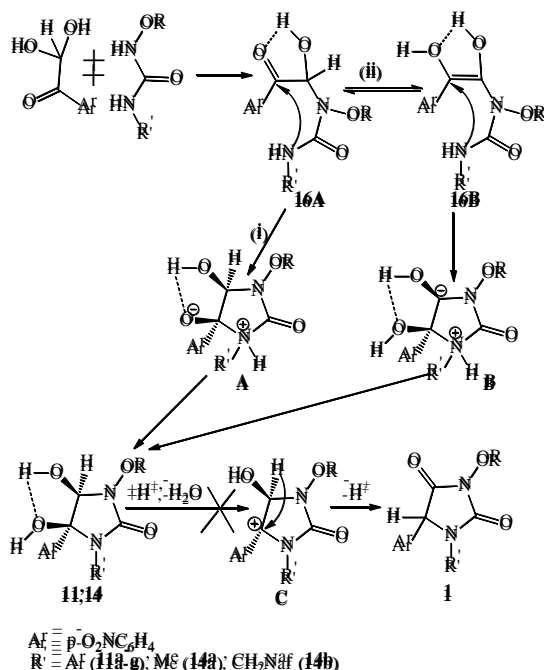
Scheme 9. The proposed mechanism of the interaction of 4-nitrophenylglyoxal with *N*-alkoxy-*N'*-arylureas and *N*-alkoxy-*N'*-alkylureas.

It is probable that the presence of such a strong electronegative substituent in 5-aryl's moiety, as nitro group, destabilizes "benzylic" cation **C** and makes impossible the further transformation of the compounds **11** and **14** into

hydantoins **1**.[9] Thus, as for the reaction of 4-nitrophenylglyoxal with *N*-alkoxy-*N'*-arylureas (**6a,e-i**) and *N*-alkoxy-*N'*-alkylureas (**13a,b**) it has been discovered that the process leads only to the mixture of diastereomers of 3-alkoxy-4,5-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-ones (**11a-g**,**12a-g**) and 3-alkoxy-1-alkyl-4,5-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-ones (**14a,b** and **15a,b**).

The diastereomer with *sic* orientation of HO-groups is the main product in both cases. The structure of 3-*n*-butyloxy-4*S*,5*S*-4,5-dihydroxy-1-(4-methylphenyl)-5-(4-nitrophenyl)-imidazolidin-2-one (**11e**) and 4*S*,5*S*-4,5-dihydroxy-1-methyl-5-(4-nitrophenyl)-3-propyloxyimidazo-lidin-2-one (**14a**) has been studied by X-ray structural analysis.

Conclusions

4-Nitrophenylglyoxal reacts with *N*-alkoxy-*N'*-arylureas (**6a,e-i**) and *N*-alkoxy-*N'*-alkylureas (**13a,b**) in acetic acid medium at the room temperature forming mainly 3-alkoxy-4,5-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-one (**11a-g**) and 3-alkoxy-1-alkyl-4,5-dihydroxy-5-(4-nitrophenyl)-imidazolidin-2-ones (**14a,b**), respectively, which have *cis* oriented hydroxyl groups. X-Ray structural analysis of 3-*n*-butyloxy-4*S*,5*S*-4,5-dihydroxy-1-(4-methylphenyl)-5-(4-nit-rophenyl)imidazolidin-2-one (**11e**) and 4*S*,5*S*-4,5-dihydroxy-1-methyl-5-(4-nitrophenyl)-3-propyloxyimidazo-lidin-2-one (**14a**) has confirmed this special structural feature of these compounds.

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DETERMINATION OF THE BEST PROBABILITY DISTRIBUTION OF FIT FOR OZONE CONCENTRATION DATA IN CAMPO GRANDE-MS-BRAZIL

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This study discussed the behavior of ozone level observed in the atmospheric region of Campo Grande. To determine the best adjusted distribution to describe the ozone co-generation data for the year 2016 in Campo Grande were used 15 functions adjusted for this purpose; the performances of the distributions are evaluated using three test qualities, namely Kolmogorov- Smirnov, Anderson-Darling and Chi-Square test. Finally, the result of the fitted quality test is compared, it was observed that the generalized extreme value distribution provides a good fit for the whole year and the distributions Gamma 3P; lognormal 3P; weibull and Gamma 3P for the seasons of the year: winter, spring, summer, autumn, which are empirically proven to be the most appropriate distribution of data.

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INTRODUCTION

The study of variable distributions as a means of understanding atmospheric phenomena to determine their occurrence patterns and to allow a reasonable predictability of the climatic behavior of a region is a valuable tool for planning and managing numerous agricultural and livestock activities, human beings. Probabilistic forecasts help in the planning and conduct of agricultural activities, by rationalizing procedures and avoiding or minimizing the possible damages caused by the action of bad weather.[1]

For Catalunha et al.[2], the use of probability density functions is directly linked to the nature of the data to which they relate. Some have good estimation capacity for small numbers of data, others require a large number of observations. Provided that the representativeness of the data is respected, the estimates of its parameters for a given region can be established as general purpose, without prejudice to the precision in the estimation of probability.

The continuous probability distributions are widely used in several probabilistic studies,[1-7] due to the adjustment of their variables, which may not be perfect, but they describe a real situation well, providing answers to the hypotheses that may have been raised in the research. According to Ferreira,[8] the random variables of the continuous distributions are those that assume their values in a real scale, modeled by a density function *f(x)* with the following properties:

a) The value of f(x) is always ≥ 0;

b) the area under the curve established by the density and bounded by the abscissa axis is equal to the unit, if the domain of variable *X* is considered.

The use of probability distribution functions requires the use of tests to prove the adaptation of the data or series of data to the functions. These tests are known as adhesion tests and their real function is to verify the shape of a distribution by analyzing the adequacy of the data to the curve of a hypothetical distribution model. According to Souza, A. and Ozonur,[1] the Chi-square, Kolmogorov-Smirnov, Lilliefors, Shapiro-Wilk, Cramer-von Mises adhesion tests serve to compare the empirical probabilities of a variable with the theoretical probabilities estimated by the distribution function under test, the sample values may come from a population with that theoretical distribution.

The objective of the present study is to evaluate the variation of stratospheric ozone over Campo Grande in the year 2016. The theory of probability distribution will be applied to analyze stratospheric ozone variation. In this respect, the adequacy of the distributions of the fifteen probability functions will be tested with the Kolmogorov-Smirnov adhesion tests, Anderson Darling. In addition, the mean and standard deviation parameters and the trend analysis for ozone variability.

Study area

Campo Grande is the capital city of South MatoGrosso (MS) state, located in the southern of Brazil Midwest region, and sited in the center of the state. Geographically the considered city is near to the Brazilian border with Paraguay and Bolivia. It is located at 20°26'34'' South and 54°38'47'' West. Fig. 1 shows a location of Campo Grande, in capital of the state of Mato Grosso (MS).

It occupies a total area of 8,096.051 km² or 3,126 mi², representing 2.26 % of the total state area, within 860,000 inhabitants (2016) and a corresponding HDI of 0.78. The urban area is approximately 154.45 km² or 60 mi², where tropical climate and dry seasons predominate, with two clearly defined seasons: warm and humid in summer, and less rainy and mild temperatures in winter. During the months of winter, the temperature can drop considerably, arriving in certain occasions to the thermal sensation of 0 ºC or 32 ºF with occasional light freezing. The yearly average precipitation is estimated at 1,534 millimeters, with small up or down variations.

The main pollution problems in the city are attributed to the traffic of vehicles, to the raise of building activities, to the presence of dumping grounds, to the use of small power generators running on oil to supply the electric grid power, and to the induced fire outbreak used to clean up local terrains.

For the development of this work, we used electronic data from the continuous air monitoring station located on the campus of the Federal University of MatoGrosso do Sul, Campo Grande (MS), as show in Fig. 1.
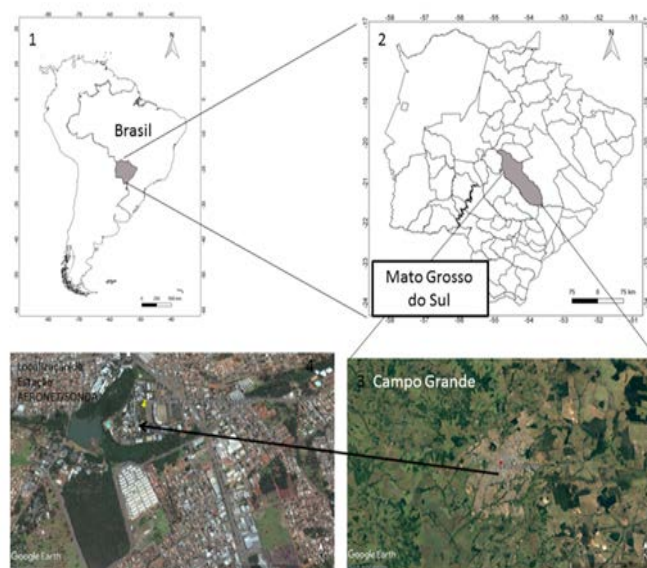
Figure 1. Location of the Municipality of Campo Grande in the State of MatoGrosso do Sul, and the continuous air monitoring station located on the campus of the Federal University of MatoGrosso do Sul, Campo Grande, MS.

Tables 1 and 2 show the instrumentation used to measure atmospheric pollutants and meteorological parameters.

Table 1. Summary of the instrumentation for measuring the atmospheric pollutants and meteorological parameters for the year 2016 in MS.

Parameter	Ozone
Instrument model	Thermo Environmental 49C
Detector	Chemiluminescence
PA Equivalent Method	EQOA-0880-047
Error (±)	1 ppb

Table 2. Shows the instrumentation used to measure atmospheric pollutants and meteorological parameters during the year 2016 in Campo Grande.

Parameter	Instrument Model	Detector	Equivalent Method Number of PAPA	Error (±)
O_3	Thermo Environmental 49C	Chemiluminescence	EQOA-0880-047	1 ppb
WS	Met One 010C	Anemometer	n.a.	1 %
WD	Met One 020C	Potentiometer	n.a.	3º
Temperature	Met One 060A	Multi-stage thermistor	n.a.	0.5 C
Pressure	Met One 090D	Barometric sensor	n.a.	1.35 mbar
RH	Met One 083E	Capacitance sensor	n.a.	2%
SR	Met One 095	Pyranometer	n.a.	1%

n.a.: not applied

Table 3. The probability density functions of selected probability distributions.

Distributions	General mathematical expression	Parameters
Exponential	$f(x) = \lambda e^{-\hat{x}}$ for $x \geq 0$	λ= shape
Exponential (2p)	$F(x : \gamma, \lambda) = (1 - e^{-\hat{x}})^2; \lambda, \gamma > 0$	λ=scale γ= shape
Gamma	$g(y) = \dfrac{\beta^\alpha}{\Gamma(\alpha)} Y^{\alpha-1} e^{-\frac{\alpha}{y}}; y \geq 0; \alpha, \beta > 0$	α=shape β=scale
Gamma (3p)	$f(t \mid \alpha, \beta, \gamma) = \dfrac{1}{\beta\Gamma(\alpha)} \left(\dfrac{t-\gamma}{\beta}\right)^{\frac{\alpha}{1}} e^{\frac{t-\gamma}{\beta}}; \alpha, \beta > 0; -\infty < \gamma < \infty; t > \lambda$	α=shape, β=scale γ= threshold
Gen. Extreme Value	$F(y) = \dfrac{1}{b}[1+H]^{1-\frac{1}{k}} e^{-(1+H)^{\frac{1}{k}}};$ where $H = \dfrac{k(y-a)}{b}$	k=shape, a =location, b=scale
Gumbel Max	$F(y) = \dfrac{1}{b} e^{-(e^{-H^*})};$ where $H^* = \dfrac{(y-a)}{b}$	a =location, b =scale
Gumbal Min	$f(x) = \dfrac{1}{\sigma}\exp(z - \exp(z)), z = \left(\dfrac{x-\mu}{\sigma}\right)$	σ=std, μ=mean
Log-Logistic	$f(x) = \dfrac{\lambda k(\lambda x)^{k-1}}{(1+(\lambda x)^k)^2},$ where $x, \lambda, k > 0$	λ=scale, κ= shape
Log-Logistic (3p)	$f(x) = \dfrac{\beta\left[\dfrac{x-\gamma}{\alpha}\right]^{\beta-1}}{\alpha\left[1+\left\{\dfrac{x-\gamma}{\alpha}\right\}^\beta\right]^2}; \alpha > 0; x > \gamma; \beta \geq 1$	α=shape, β=scale, γ=location
Logistic	$f(x) = \dfrac{e^x}{\left(1+e^x\right)^2}; x \in R$	σ=std, μ= mean
Lognormal	$f(x) = \dfrac{1}{x\sigma\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{\ln x - \mu}{\sigma}\right)^2}; x \geq 0$	σ= std, μ=mean
Lognormal (3p)	$f(x : \mu, \sigma, \gamma) = \dfrac{1}{(x-\gamma)\sigma\sqrt{2\pi}} \exp\left\{-\dfrac{1}{2}\left(\dfrac{\ln(x-\gamma)-\mu}{\sigma}\right)^2\right\}; 0 \leq \gamma < x; -\infty < \mu < \infty; \sigma > 0$	σ=std, μ=mean, γ=threshold
Normal	$f(x) = \dfrac{1}{\sigma\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{x-\mu}{\sigma}\right)^2}; -\infty < x < \infty;$	σ=std. μ=mean
Weibull	$f_x(x) = \dfrac{\alpha}{\beta}\left(\dfrac{\alpha-\gamma}{\beta}\right)^{\alpha-1} e^{\left(\frac{x-\gamma}{\beta}\right)^\alpha}; x > \mu, \alpha, \beta > 0$	β= shape θ=scale
Weibull (3P)	$f_x(x : \beta, \theta) = \beta\theta^\beta x^{\beta-1} e^{(x\theta)^\beta}; x > \mu, \alpha, \beta > 0$	α=shape, β=scale, γ=location

METHODOLOGY

To describe the amount of hourly/daily/monthly data, you need to identify the distributions that best fit the data. In this study, fifteen probability distributions are considered to test fit quality. The probability density function of the above distribution is shown in Table 3 below.

Goodness-of-Fit tests (GOF)

GOF is used to determine the best model among the distributions tested in O_3 characteristic. The goodness-of-fit test is performed in order to test the following hypothesis:

H_0 : The amount of monthly O_3 data follows the specified distribution

H_1 : The amount of monthly O_3 data does not follow the specified distribution

A couple of goodness-of-fit test have been conducted such as Kolmogorov-Smirnov test, Anderson-Darling test along with the chi-square test at significance level (α=0.05) for choosing the best probability distribution.[9]

Kolmogorov-Smirnov test

The Kolmogorov-Smirnov test[10] is used to decide if a sample comes from a population with a specific distribution.

The Kolmogorov-Smirnov (K-S) test is based on the empirical distribution function (ECDF). Given N ordered data points $Y_1, Y_2, ..., Y_N$, the ECDF is defined as

$$E_N = \frac{n(i)}{N}$$

where, $n(i)$ is the number of points less than Y_i and the Y_i are ordered from smallest to largest value. This is a step function that increases by $1/N$ at the value of each ordered data point.

Test Statistic: The Kolmogorov-Smirnov test statistic is defined as

$$D = \max_{1 \leq i \leq N}\left[F(Y_i) - \frac{i-1}{N}, \frac{i}{N} - F(Y_i) \right]$$

where F is the theoretical cumulative distribution of the distribution being tested which must be a continuous distribution (i.e., no discrete distributions such as the binomial or Poisson), and it must be fully specified (i.e., the location, scale, and shape parameters cannot be estimated from the data).

The hypothesis regarding the distributional form is rejected if the test statistic, D, is greater than the critical value obtained from a table.

Anderson –Darling test

The Anderson-Darling test[11] is used to test if a sample of data comes from a population with a specific distribution. It is a modification of the Kolmogorov-Smirnov (K-S) test and gives more weight to the tails than does the K-S test. The K-S test is distribution free in the sense that the critical values do not depend on the specific distribution being tested. The Anderson-Darling test makes use of the specific distribution in calculating critical values. This has the advantage of allowing a more sensitive test and the disadvantage that critical values must be calculated for each distribution. Currently, tables of critical values are available for the normal, lognormal, exponential, Weibull, extreme value type I, and logistic distributions.

The Anderson-Darling test statistic is defined as

$$A^2 = -N - \frac{1}{N}\sum_{i=1}^{N} (2i-1)\left[\ln F(X_i) + \ln(1 - F(X_{N\text{-}i+1}))\right]$$

where F is the cumulative distribution function of the specified distribution. Note that the Y_i are the ordered data.

The critical values for the Anderson-Darling test are dependent on the specific distribution that is being tested. Tabulated values and formulas have been published[11] for a few specific distributions (normal, lognormal, exponential, Weibull, logistic, extreme value type 1). The test is a one-sided test and the hypothesis that the distribution is of a specific form is rejected if the test statistic, A, is greater than the critical value.

Chi-square test

The Chi-square test assumes that the number of observations is large enough so that the chi-square distribution provides a good approximation as the distribution of test statistic. The Chi-squared statistic is defined as:

$$\chi^2 = \sum_{i=1}^{k} \frac{(O_i - E_i)^2}{E_i}$$

where, O_i=observed frequency; E_i=expected frequency; 'i'= number observations (1, 2, ……k), calculated by E_i= $F(X_2)$ – $F(X_1)$, and F=the CDF of the probability distribution being tested. The observed number of observation (k) in interval 'i' is computed from equation given below, and k= 1+log2n, n=sample size.

This equation is for continuous sample data only and is used to determine if a sample comes from a population with a specific distribution [9].

RESULT AND DISCUSSION

Tables 4 and 5 show the mean values and instrumentation used to measure atmospheric pollutants and meteorological parameters. The wind speed was higher in spring and lower in the summer/ fall/ winter, with the average rate slighty lower than the normal climatological, the average speed was 1.90 m s^{-1} with a minimum of 0.1 m s^{-1} and a maximum of 7.90 m s^{-1}. The atmospheric pressure was higher in autumn and winter, with values slightly below normal climatological. The average temperatures (Table 4) presented similar behaviour to the climatological normals. Temperatures (mean, maximum, and minimum) in the summer were about 9-10 °C higher than those in the winter. The mean maximum daily temperature in measurment was 26 °C and 21 °C, while the average daily minimum temperature in summer was 21 °C and 12 °C in winter. This same interval between maximum and maximumdaily temperatures was observe in all seasons. The relative humidity was slightly below normal climatological, and did not show much variation between the different seasons.However, the variation between daily averages of maximum and minimum relative humidity was 46 % in summer and 38 % in winter.

The ozone concentration (O_3) are peaks in July, August, September, October, November and December, decreasing in other months of the year. The velocity and direction of the winds is also a factor that influences the concentration of ozone, since it takes chemical species from one region to another, so regions that do not pollute can also suffer from high concentration of ozone.[12]

The maximum value reached by O_3in this time series was 79.9 ppb and the minimum 1.2 ppb. The average was 16.1ppb. It should be noted that this pollutant was measured at 359 days in 24 hours during the study period from January to December 2016 and was limited in the air quality standard of 80 ppb (CONAMA Resolution no.003/2008)[13] and with decreasing trend.

As shown in Fig. 3, it can be observed that the concentration of O_3 presented the following behaviour: maximum valuesduring the day, reaching its maximum value from 13 to 18 h and minimum values at night 26.22 ppb at 5:00 p.m., and the minimum value of 10.6 ppb at 7:00 p.m., with a dailyhourly average of 15.86 ppb. The average concentration of O_3 can vary greatly from one day to the next, since the daily variations depend on meteorological conditions, such as the presence of clouds, solar radiation, rain and wind.[14]

Asymmetry is defined as an indicator that applies to distribution analysis as a sign of irregularity and deviation from the normal distribution.[15] From Table 2, the positive asymmetry indicates a signal of allocation of the ozone concentration on the right.

Table 4. Meteorological data for the sampling period (2016).

Variables		Units	summer	autumn	winter	spring
	min	°C	21.59	14.70	12.74	15.68
TEMPERATURE	ave	°C	25.22	22.51	22.82	25.61
	max	°C	28.25	26.10	42.00	30,36
	min	%	29.80	30.80	14.90	32.80
HUMIDITY	ave	%	77.95	82.81	79.52	88.24
	max	%	98.40	98.50	98.50	98.40
	min	mbar	907.00	905.70	904.30	903.30
PRESSURE	ave	mbar	912.99	915.49	914.57	912.48
	max	mbar	918.60	925.80	919.90	919.20
	min	m s^{-1}	0.20	0.10	0.10	0.10
VV	ave	m s^{-1}	1.93	1.77	1.75	2.16
	max	m s^{-1}	6.40	7.60	7.50	6.70
	min	graus	10.30	4.30	6.60	7.90
DV	ave	graus	158.18	149.06	138.46	140.37
	max	graus	347.9	354.00	354.00	350.60
	min	W m^{-2}	0	0	0	0
RADG	ave	W m^{-2}	169.62	96.58	125.30	116.68
	max	W m^{-2}	973.50	839.50	793.60	935.90
	min	W m^{-2}	0	0	0.01	0
UV	ave	W m^{-2}	7.60	3.83	4.14	5.30
	max	W m^{-2}	40.26	28.85	28.27	34.23

Source: CEMTEC-MS

This result stated that mainly of values is determined in left and extreme values of the right of the mean. Kurosis illustrates the vertical peak or the softness of a distribution compared to the normal distribution. In our case, kurtosis is seasonally negative. The negative kurtoz stated a rather smooth, large broad peak distribution as shown in frequency histograms. Positive kurtosis here indicated a peak distribution as shown for seasonal months and during the whole of Fig. 4 representing more dynamic andintermittent ozone levels. The coefficient of variation is also quite irregular and large.

It was found that the distribution of the ozone concentration data was positively distorted. The data set indicates that a coefficient of variation of the ozone concentration is around 47-77 % in Campo Grande.

Test statistics for the Kolmogorov-Smirnov (*D*) test, Anderson-Darling test (A_2) and chi-square test for ozone concentration data were calculated for fifteen probability distributions. The probability distribution with their ranks along with its test statistic is presented in Table 5.

According to Kolmogorov-Smirnov test (D), Anderson-Darling (AD) and Chi-square test it is observed that generalized extreme value distribution considered as a good fit to the ozone concentration data of Campo Grande station as shown in Table 6.

It is also observed that some of the probability distributions have the same rank in Kolmogorov-Smirnov, Anderson-Darling and Chi-square tests. These distributions are Gumel Max., Lognormal (3p) and Weibull (3p).

Table 5. The statistical parameters for ozone concentration are summarized in Table 5. 2016.

2016	Jan.	Febr.	March	Apr.	May	June
Mean	21.6	16.46	16.75	16.7	13.23	11.28
St. dev	11.45	9.09	9.36	9.73	7.06	7.69
C variation	53	55.26	55.89	58.27	53.38	68.15
Median	18.9	15.25	15.8	15.5	13.2	10.2
Minimum	1.9	2.2	2.2	2.1	2	2
Maximum	79.7	70.9	58.5	61.2	41.3	34.5
Skewness	1.13	1.39	0.96	1.11	0.4	0.38
Kurtosis	2,11	4,98	1,49	1,95	0,11	-1,04
Count	742	672	742	742	742	720

2016	July	Aug.	Sept.	Oct.	Nov.	Dec.
Mean	12.41	17.01	18.88	16.94	16.11	15.97
St. dev	8.04	13.2	11.06	8.83	7.75	7.61
C variation	64.76	77.6	58.57	52.13	48,1	47.66
Median	12.1	15.55	17.6	15.8	15.2	14.75
Minimum	2	1.6	2	2	2.3	1
Maximum	44.4	55.9	57.7	47.7	46.6	36.4
Skewness	0.47	0.65	0.71	0.71	0.67	0.42
Kurtosis	-0.32	-0.44	0.38	0.47	0.44	-0.54
Count	742	742	720	742	720	742
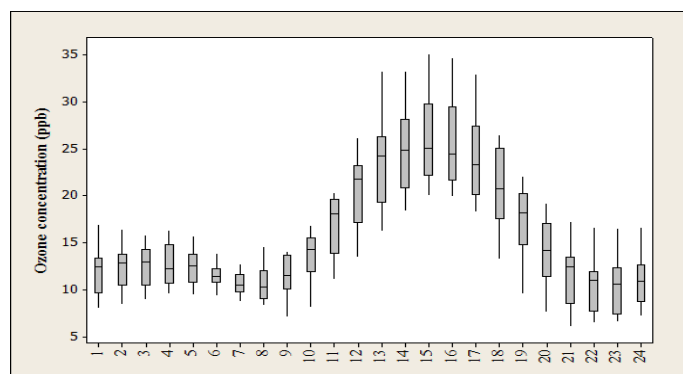
Figure 3. Graph of the average hourly variation of the ozone concentration for the year 2016.

Table 6. Criteria for the quality adjustment of historical series of ozone concentration (ppb), for the year 2016, for the fifteen models of probability distribution using different goodness of fit test.
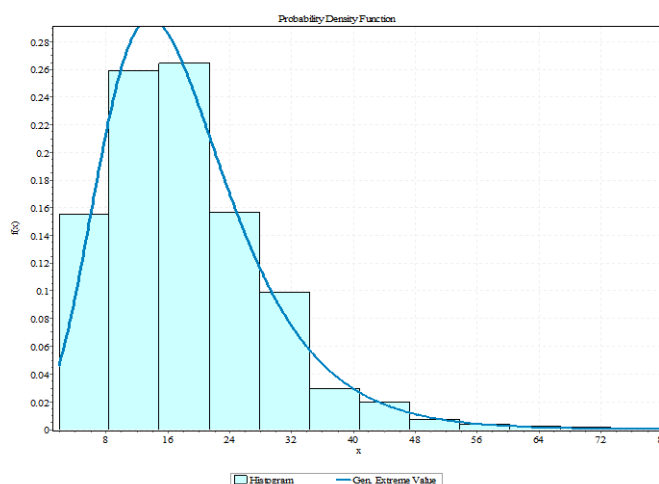
Distribution	Kolmogorov Smirnov		Anderson Darling		Chi-Squared	
	Statistic	Rank	Statistic	Rank	Statistic	Rank
Exponential	0.21904	15	200.67	15	973.8	14
Exponential (2p)	0.18435	14	135.99	13	649.02	13
Gamma	0.0294	7	2.3921	5	20.793	6
Gamma (3p)	0.0283	6	1.6752	4	20.611	5
Gen. extreme value	0.01506	1	0.71946	1	8.1498	1
Gumbel Max	0.01509	2	0.73148	2	8.4675	2
Gumbal Min	0.14531	13	150.42	14	N/A	
Log-Logistic	0.06573	9	16.385	9	121.45	11
Log-Logistic (3p)	0.02544	4	2.4409	6	23.276	7
Logistic	0.07628	12	22.787	11	94.74	9
Lognormal	0.06939	10	19.438	10	116.65	10
Lognormal (3p)	0.02024	3	1.1364	3	9.234	3
Normal	0.7602	11	24.952	12	122.19	12
Weibull	0.02661	5	2.6328	7	15.411	4
Weibull (3P)	0.03659	8	3.5304	8	24.631	8

The identified distributions are listed in Table 7 with the estimated parameters for ozone concentration data set. Fig.4 showed the behavior of selected best fitted probability density function of average ozone concentration over Campo Grande. The estimated parameters were used to generate random numbers for the ozone concentration and the least squares method was used for ozone analysis.

Table 7. Estimation of parameters of identified probability distribution for the year 2016.

#	Distribution	Parameters
1	Exponential	$\lambda=0.0546$
2	Exponential (2P)	$\lambda=0.06092$ $\gamma=1.9$
3	Gamma	$\alpha=3.1491$ $\beta=5.816$
4	Gamma (3P)	$\alpha=3.4272$ $\beta=5.5806$ $\gamma=-0.8105$
5	Gen. Extreme Value	$k=-0.00334$ $\sigma=8.0446$ $\mu=13.698$
6	Gumbel Max	$\sigma=8.0472$ $\mu=13.67$

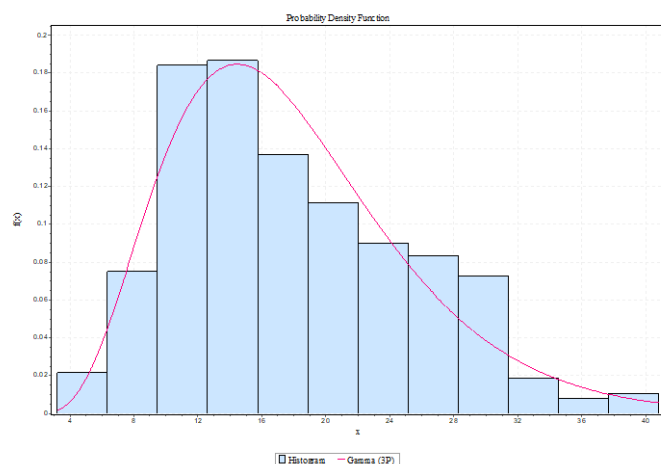| 7	Gumbel Min	$\sigma=8.0472$ $\mu=22.96$
8	Log-Logistic	$\alpha=2.8062$ $\beta=15.4$
9	Log-Logistic (3P)	$\alpha=4.3462$ $\beta=23.336$ $\gamma=-6.8008$
10	Logistic	$\sigma=5.6902$ $\mu=18.315$
11	Lognormal	$\sigma=0.63107$ $\mu=2.7351$
12	Lognormal (3P)	$\sigma=0.37696$ $\mu=3.2085$ $\gamma=-8.2426$
13	Normal	$\sigma=10.321$ $\mu=18.315$
14	Weibull	$\alpha=2.0108$ $\beta=20.506$
15	Weibull (3P)	$\alpha=1.6753$ $\beta=18.808$ $\gamma=1.4965$

Figure 4. Graph of the histogram of best fitted probability density function for the average monthly concentration of ozone of the year 2016.

Table 8. Criteria for the quality adjustment of historical series of ozone concentration (ppb), for the winter season for the year 2016.

| Distribution	Kolmogorov Smirnov		Anderson Darling		Chi-Squared	
	Statistic	Rank	Statistic	Rank	Statistic	Rank
Exponential	0.3199	15	120.35	15	653.44	14
Exponential (2p)	0.2602	14	82.843	14	393.81	14
Gamma	0.0592	6	2.8732	4	28.591	3
Gamma (3p)	0.0508	2	2.3264	1	25.803	2
Gen. Extreme Value	0.0575	5	2.9367	5	29.736	4
Gumbel Max	0.0595	7	4.2931	8	33.123	6
Gumbal Min	0.1453	13	42.145	13	238.99	13
Log-Logistic	0.0646	8	4.8025	9	33.452	8
Log-Logistic (3p)	0.0515	4	3.7942	7	33.4	7
Logistic	0.0118	12	13.627	12	115.14	12
Lognormal	0.0471	1	2.4621	2	23.532	1
Lognormal (3p)	0.0512	3	2.7018	3	29.89	5
Normal	0.0987	11	9.7242	10	98.931	11
Weibull	0.0944	10	9.8624	11	80.259	10
Weibull (3P)	0.0651	9	3.2715	6	36.002	9

Table 9. Determination of the parameters of the statistical test probability functions for winter season in the year 2016.

#	Distribution	Parameters
1	Exponential	λ=0.055584
2	Exponential (2P)	λ=0.06799 γ=3.2
3	Gamma	α=5.9432 β=3.0132
4	Gamma (3P)	α=4.6386 β=3.4673 γ= 1.8252
5	Gen. Extreme Value	k=-0.04606 σ=6.2094 μ=14.596
6	Gumbel Max	σ=5.7276 μ=14.602
7	Gumbel Min	σ=5.7276 μ=21.214
8	Log-Logistic	α=4.1568 β=16.402
9	Log-Logistic (3P)	α=1.1008 β=16.853 γ=-0.293
10	Logistic	σ=4.05 μ=17.908
11	Lognormal	σ=0.42534 μ=2.7986
12	Lognormal (3P)	σ=0.34214 μ=3.0125 γ=-3.6292
13	Normal	σ=7.3459 μ=17.908
14	Weibull	α=2.9233 β=19.958
15	Weibull (3P)	α=2.1529 β=16.829 γ=3.0372

Figure 5. Graph of the histogram of ozone concentration for best fitted probability density function of winter season during the year 2016.

Table 10. Comparison of historical series of ozone concentration (ppb), for the spring season for the year 2016

Distribution	Kolmogorov Smirnov		Anderson Darling		Chi-Squared	
	Statistic	Rank	Statistic	Rank	Statistic	Rank
Exponential	0.2929	15	103.36	15	535.99	14
Exponential (2p)	0.2384	14	68.54	14	335.52	14
Gamma	0.0418	7	1.57	7	21.577	8
Gamma (3p)	0.0385	5	1.303	4	20.477	7
Gen. Extreme Value	0.0342	3	1.151	3	17.941	5
Gumbel Max	0.0388	6	1.469	5	16.808	4
Gumbal Min	0.1717	13	58.084	13	248.92	13
Log-Logistic	0.0424	8	1.793	8	15.541	3
Log-Logistic (3p)	0.0368	4	1.529	6	13.239	1
Logistic	0.1123	12	13.679	12	200.27	12
Lognormal	0.0309	1	1.148	2	14.736	2
Lognormal (3p)	0.0332	2	1.085	1	18.398	6
Normal	0.0101	11	12.294	11	987.585	11
Weibull	0.0808	10	8.815	10	70.441	10
Weibull (3P)	0.0521	9	2.943	9	32,796	9
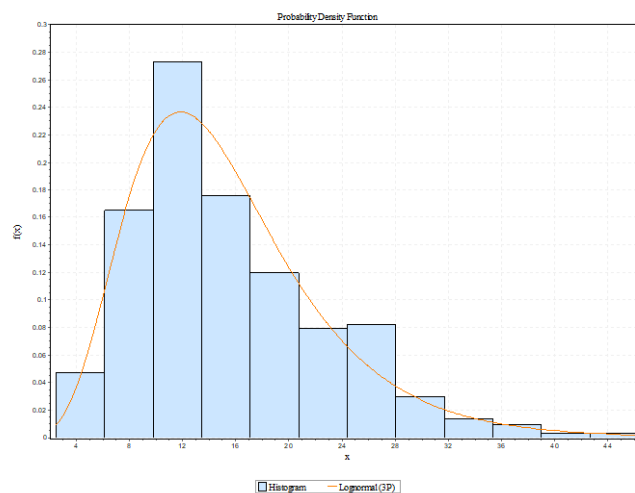
Figure 6. Graph of the histogram of ozone concentration for best fitted probability density function of spring season during the year 2016.

Table 11 Determination of the parameters of the statistical test probability functions for spring season in the year 2016.

| #	Distribution	Parameters
1	Exponential	λ=0.06462
2	Exponential (2P)	λ=0.07707 γ=2.5
3	Gamma	α=4.5797 β=3.3792
4	Gamma (3P)	α=4.0702 β=3.5711 γ= 0.94067
5	Gen. Extreme Value	k=-0.02238 σ=5.6045 μ=12.114
6	Gumbel Max	σ=5.6385 μ=12.221
7	Gumbel Min	σ=5.6385 μ=18.73
8	Log-Logistic	α=3.7051 β=13.8847
9	Log-Logistic (3P)	α=3.9508 β=15.06 γ=-1.0121
10	Logistic	σ=3.987 μ=15.476
11	Lognormal	σ=0.4805 μ=2.6297
12	Lognormal (3P)	σ=0.3784 μ=2.860 γ=-3.2736
13	Normal	σ=7.2316 μ=15.476
14	Weibull	α=2.6056 β=17.258
15	Weibull (3P)	α=1.9116 β=14.859 γ=2.3114

Table 12. Criteria for the quality adjustment of historical series of ozone concentration (ppb), for the summer season for the year 2016.

Distribution	Kolmogorov Smirnov		Anderson Darling		Chi-Squared	
	Statistic	Rank	Statistic	Rank	Statistic	Rank
Exponential	0.1805	15	51.143	15	203.73	15
Exponential (2p)	0.1274	13	21.589	13	109.27	13
Gamma	0.0555	7	4.895	7	31.863	7
Gamma (3p)	0.0485	4	3.452	5	24.564	4
Gen. Extreme Value	0.0437	2	2.855	3	18.869	3
Gumbel Max	0.0591	8	5.076	8	32.838	8
Gumbal Min	0.1489	14	42.117	14	153.17	14
Log-Logistic	0.0710	10	8.655	11	57.986	11
Log-Logistic (3p)	0.0523	5	4.384	6	31.581	6
Logistic	0.0944	12	12.391	12	63.343	12
Lognormal	0.0656	9	8.103	9	53.245	10
Lognormal (3p)	0.0532	6	3.194	4	26.333	5
Normal	0.0819	11	8.622	10	43.568	9
Weibull	0.0432	1	2.035	1	15.086	1
Weibull (3P)	0.0452	3	22.742	2	16.461	2

Table 13. Determination of the parameters of the statistical test probability functions for **summer** season in the year 2016.

#	Distribution	Parameters
1	Exponential	λ=0.07373
2	Exponential (2P)	λ=0.08698 γ=2.0667
3	Gamma	α=2.9589 β=4.584
4	Gamma (3P)	α= 2.0913 β=6.027 γ= 0.95965
5	Gen. Extreme Value	k=-0.05615 σ=6.7483 μ=10.025
6	Gumbel Max	σ=6.148 μ=10.015
7	Gumbel Min	σ=6.148 μ=18.73
8	Log-Logistic	α=2.5158 β=11.044
9	Log-Logistic (3P)	α=3.5158 β=15.698 γ=-3.6977
10	Logistic	σ=4.3473 μ=13.564
11	Lognormal	σ=0.6897 μ=2.4036
12	Lognormal (3P)	σ=0.4129 μ=2.8897 γ=-5.9785
13	Normal	σ=7.8851 μ=13.564
14	Weibull	α=1.8089 β=115.166
15	Weibull (3P)	α=1.4771 β=13.186 γ=1.5853

Now, probe the behaviour of ozone level on the basis of seasons.Tables 8, 9 and Fig. 5 (winter season); Tables 10, 11 and Fig. 6 (spring season); Tables12, 13 and Fig. 7 (summer season) and Tables 14, 15 and Fig. 8 (autumn season) show the summary of the komolgorov Smirnov suitability test, Anderson-Darling (AD), Chi Squared together with the estimates of the parameters of the various candidate models for the seasons of the year.
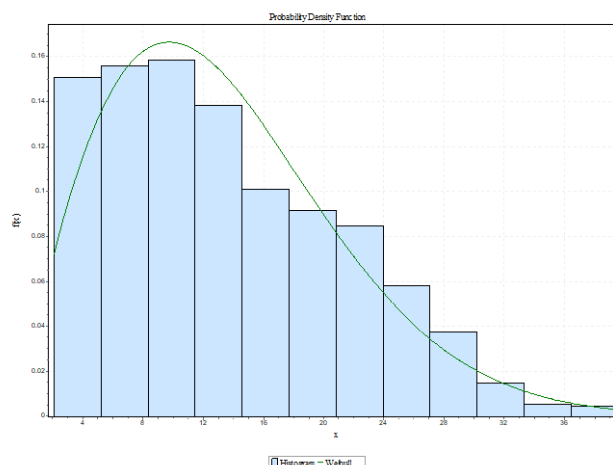
Figure 7. Graph of the histogram of ozone concentration for best fitted probability density function of summer season during the year 2016**.**

Table 14. Criteria for the quality adjustment of historical series of ozone concentration (ppb), for the autumn season for the year 2016

Distribution	Kolmogorov Smirnov		Anderson Darling		Chi-Squared	
	Statistic	Rank	Statistic	Rank	Statistic	Rank
Exponential	0.3278	15	131.030	15	728.82	15
Exponential (2p)	0.2363	14	76.684	14	370.21	14
Gamma	0.0283	4	0.725	3	9.735	5
Gamma (3p)	0.0258	1	0.592	1	6.301	2
Gen. Extreme Value	0.0281	2	0.687	2	8.131	4
Gumbel Max	0.0406	8	2.406	8	21.788	9
Gumbal Min	0.1491	13	39.767	13	149.27	13
Log-Logistic	0.0490	9	2.445	9	14.227	8
Log-Logistic (3p)	0.0359	6	1.499	6	11.696	6
Logistic	0.0806	12	7.926	12	51.827	12
Lognormal	0.0301	5	1.518	7	5.836	1
Lognormal (3p)	0.0283	3	0.747	4	8.031	3
Normal	0.0784	11	5.888	10	48.588	10
Weibull	0.0667	10	6.169	11	49.879	11
Weibull (3P)	0.0389	7	0.802	5	13.064	7

Table 15. Determination of the parameters of the statistical test probability functions for **autumn** season in the year 2016.

#	Distribution	Parameters
1	Exponential	λ=0.05827
2	Exponential (2P)	λ=0.07754 γ=4.2667
3	Gamma	α=6.7873 β=2.5287
4	Gamma (3P)	6.02 β=2.7226 γ= 0.7726
5	Gen. Extreme Value	k=-0.07782 σ=5.7112 μ=14.277
6	Gumbel Max	σ=5.1365 μ=14.198
7	Gumbel Min	σ=5.1365 μ=20.128
8	Log-Logistic	α=4.4137 β=15.874
9	Log-Logistic (3P)	α=5.3741 β=19.808 γ=-3.5914
10	Logistic	σ=3.632 μ=17.163

11	Lognormal	$\sigma=0.40187$ $\mu=2.766$
12	Lognormal (3P)	$\sigma=0.2738$ $\mu=3.1397$ $\gamma=-6.8111$
13	Normal	$\sigma=6.5878$ $\mu=17.163$
14	Weibull	$\alpha=3.1179$ $\beta=19.081$
15	Weibull (3P)	$\alpha=2.1068$ $\beta=14.886$ $\gamma=3.9828$
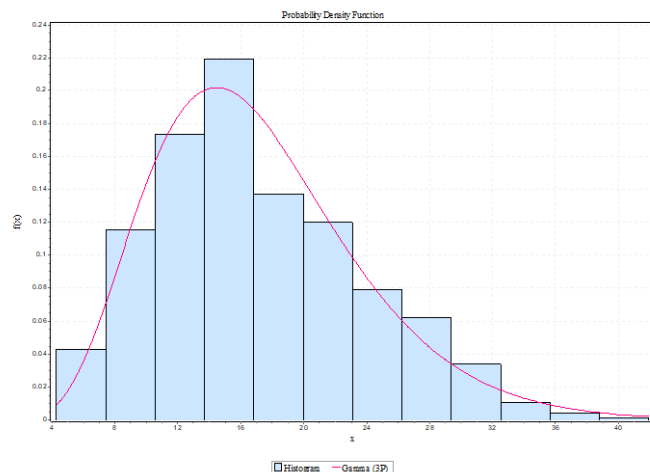
Figure 8. Graph of the histogram of ozone concentration for best fitted probability density function of autumn season during the year 2016

The selection of the best fit distribution was made based on the AD statistics and p value. A distribution with the highest p value and the lowest AD statistic is selected as the best distribution. Based on the above criteria, the best fit distributions for the datasets were identified. Thus, the best distribution for the four datasets (winter, spring, summer, autumn) is Gamma 3P; lognormal 3P; weibull and Gamma 3P.

The pdf for the best fit distributions for the four data sets is shown in Figs. 5, 6, 7 and 8. The pdf also shows the corresponding line for the mean ozone concentration of 8 hours; This clearly shows that the ozone pattern is violated during the different seasons of the year. However, the tail of the distribution is long in the case of summers.

CONCLUSIONS

A systematic evaluation procedure was applied to evaluate the performance of different probability distributions in order to identify the best fit probability distribution for the Campo Grande ozone concentration data. It was observed that the generalized extreme value distributionprovides a good fit for the whole year and the distributions: Gamma 3P; lognormal 3P; weibull and Gamma 3P for the seasons of the year: winter, spring, summer, autumn. The identification of the amount of ozone concentration data can have a wide range of applications in agriculture, engineering design and climate research.

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A NEW KEY FOR OLD LOCK: GLYCEROL, AS AN OH-ACID, CATALYZED ONE-POT THREE-COMPONENT AND FULLY GREEN SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2(1H)-ONE AND -THIONES

S. Golshani Anvar[a] and F. K. Behbahani[a]*

Keywords: Organic OH-acid, reusable catalyst, glycerol, dihydropyrimidin-2(1H)thione, dihydropyrimidin-2(1H)one.

Synthesis of 3,4-dihydropyrimidin-2(1H)-one and 3,4-dihydropyrimidin-2(1H)-thione derivatives from aldehydes, ethyl acetoacetate and urea or thiourea using glycerol as an organo OH-acid, green and reusable catalyst is reported. The practical and simple protocol led to excellent yields of the dihydropyrimidin-2(1H)-one and thiones under mild reaction conditions and within short span of reaction times with easy reaction workup by maintaining excellent atom economy.

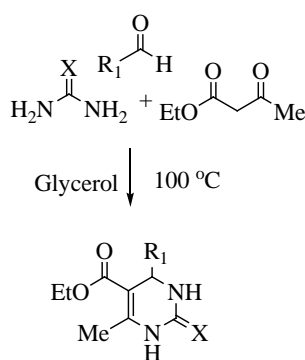*Corresponding Authors
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INTRODUCTION

Aryl-3,4-dihydropyrimidines derivatives (DHPMs) have received great attention because of their wide range of therapeutic and pharmacological properties, such as antiviral,[7] antitumor, antibacterial and antifungal,[8] anti-inflammatory,[9] antihypertensive agents, and neuropeptide Y (NPY) antagonists.[10] Furthermore, these compounds have emerged as the integral backbones of several calcium-channel blockers.[11] Also, several alkaloids containing the dihydropyrimidine were isolated from marine sources, for example, of these are the batzelladine alkaloids, which are found to be potent HIVgp-120-CD4 inhibitors.[12,13] After the classic Biginelli approach to 3,4-dihydropyrimidinones, the development of multistep synthetic strategies that produce relatively higher yields was demand. So, various protocols for synthesis of 3,4-dihydropyrimidines were explored by varying components and catalysts.[14]

Scheme 1. Preparation of DHPMs in glycerol as a solvent.

In this communication, we report glycerol as an organic OH-acid, green and reusable catalyst for the synthesis of DHPMs via a one-pot three component condensation of aldehydes, ethyl acetoacetate, urea and thiourea at 100 °C (Scheme 1).

EXPERIMENTAL

Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. IR spectra were recorded on a Perkin Elmer FT-IR spectrometer between 4000-400 cm^{-1}. ^{1}HNMR spectra were obtained on Bruker DRX- 300 MHZ NMR instrument. Analytical TLC of all reactions was performed on Merck precoated plates (silica gel 60 F-254 on aluminium). Elemental analyses of the new products were done using a Vario EL III apparatus. Their results are in good agreement with the calculated values.

General procedure for the synthesis of arylidene pyrimidinones using glycerol

A mixture of the 2.0 mmol aldehyde, 2.0 mmol, 0.26 g ethyl acetoacetate (2.0 mmol), 5.0 mmol, 0.072 g or 0.0913 g urea or thiourea and 1 cm^3 glycerol was heated in an oil bath at 100 °C for the specified times. The reaction was monitered by TLC (ethyl acetate/n-hexane, 1:2). After completion of the reaction, crushed ice was added and stirred for 10 min. The product was collected by filtration, washed with water and then crystallized from methanol to afford the pure product.

Ethyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

IR [KBr] υ(cm^{-1}): 3331, 3101, 2966, 1710, 1689, 1631, 1525, 1456, 1347, 1317, 1266, 1225, 1088, 901, 808, 794, 739, 685. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ: 1.11 (t, J = 7.5 Hz, 3H), 2.26 (s, 3H), 4.01 (q, J = 7.5 Hz, 2H), 5.28 (d, J = 3.0 Hz, 1H), 7.61-7.70 (m, 2H), 7.87 (s, 1H, NH), 8.07-8.13 (m, 2H), 9.34 (s, 1H, NH).

Ethyl 4-(4-(dimethylamino)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

IR [KBr] υ(cm^{-1}): 3246, 3116, 2926, 1721, 1702, 1650, 1527, 1457, 1366, 1289, 1222, 1169, 1093, 785. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ: 1.12 (t, J = 7.5 Hz, 3H, CH$_3$), 2.21(s, 3H, CH$_3$), 2.83 (s, 6H, N(CH$_3$)$_2$), 4.0 (q, J = 7.5 Hz, 2H, -OCH$_2$), 5.02 (s, 1H, CH), 6.65 (d, J = 9.1 Hz, 2H, arom), 7.03 (d, J = 9.1 Hz, 2H, arom), 7.55 (s, 1H, NH), 9.0 (s, 1H, NH).

Ethyl 4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

IR [KBr] υ(cm^{-1}): 3347, 2982, 1698, 1650, 1489, 1370, 1332, 1302, 1263, 1211, 1122, 1096, 1050, 1022, 806, 750, 730. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ: 2.2 (t, J = 7.0 Hz, 3H), 3.6 (s, 3H), 3.8 (q, J = 7.0 Hz, 2H), 6.1 (d, J = 3.0 Hz, 2H), 6.3 (q, J = 2 Hz, 1H), 7.6 (s, 1H), 7.8 (s, 1H, NH), 9.3 (s, 1H, NH).

Ethyl (E)-6-methyl-2-oxo-4-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxylate

IR [KBr] υ(cm^{-1}): 3244, 3113, 2977, 1723, 1652, 1451, 1286, 1228, 1095, 967, 778, 692. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ: 1.21 (t, J = 7.0 Hz, 3H), 2.34 (s, 3H), 4.11 (q, J = 7.05 Hz, 2H), 4.73 (d, J = 4.80 Hz, 1H), 6.21 (d, J = 6.0 Hz, 1H), 6.37 (d, J = 15.9 Hz, 1H), 7.19-7.40 (m, 5H), 7.52 (s, 1H, NH), 9.11 (s, 1H, NH).

Ethyl 4-(2-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

IR [KBr] υ(cm^{-1}): 3364, 3166, 3084, 2948, 1727, 1610, 1589, 1564, 1491, 1475, 1371, 1323, 1223, 1187, 1152. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ: 1.04 (t, J = 7.2 Hz, 3H), 2.15 (s, 3H), 4.10 (d, 1H), 4.22 (q, J = 7.2 Hz, 2H), 4.22 (s, 1H), 6.81-7.21 (m, 4H), 8.46 (s, 1H, NH), 9.57 (s, 1H, NH).

Ethyl 4-(4-(dimethylamino)phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

IR [KBr] υ(cm^{-1}): 3296, 3177, 2989, 1662, 1575, 1523, 1458, 1370, 1332, 1287, 1180, 1113, 943, 814, 771, 572. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ: 1.11 (t, J = 7.0 Hz, 3H), 2.28 (s, 3H), 2.85 (s, 6H), 3.97 (q, J = 7.0 Hz, 2H), 5.04 (d, J = 3.2 Hz, 1H) 6.66 (d, J = 8.5 Hz, 2H), 7.01 (d, J = 8.5 Hz, 2H), 9.55 (s, 1H, NH), 10.24 (s, 1H, NH).

**Ethyl 6-methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate**

IR [KBr] υ(cm^{-1}): 3087, 2987, 1729, 1661, 1628, 1528, 1400, 1351, 1299, 1209, 1103, 1045, 1019, 812, 734, 678. ^{1}H NMR (250 MHz, DMSO-d$_6$) δ: 1.13 (t, J = 7.1 Hz, 3H), 2.34 (s, 3H), 4.05 (q, J = 7.1Hz, 2H), 5.36 (d, J = 3.6 Hz, 1H), 7.70-7.72 (m, 2H), 8.10-8.11 (m, 1H), 8.17-8.20 (m, 1H), 9.81 (s, 1H, NH), 10.55 (s, 1H, NH).

RESULTS AND DISCUSSION

On basis of our previous investigation that synthesis of dihydropyrimidinones need to temperature and acidic condition as mention in introduction section. Thus the authors decided to set up a model reaction to achieve a fully green procedure for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-one and -thione derivatives in the presence of glycerol as green solvent and organic OH-acid catalyst.

Then the synthesis of compound 5-(ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-ones(Table 1) was selected as a model reaction to determine suitable reaction conditions. The reaction was carried out by employing benzaldehyde (2.0 mmol), ethyl acetoacetate (2.0 mmol),urea (5.0 mmol) and different amount of glycerol (5.0, 4.0, 3.0 and 1.0 ml) at 100 °C. Found that increasing amount of glycerol does not effect to yield and rection time, therefore, we selected 1.0 ml of glycerol as green organic OH-acid catalyst for this reaction. To generalize of this method the reaction of ethyl acetoacetate with different kinds of aromatic aldehydes and urea/thiourea using glycerol as catalyst at 100 °C was examined.
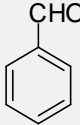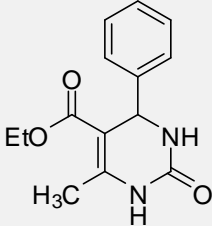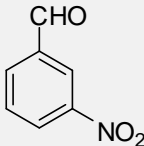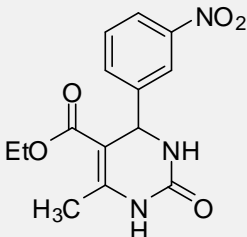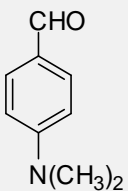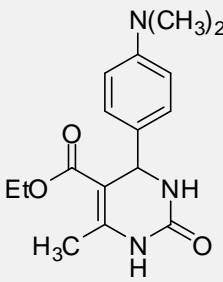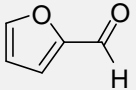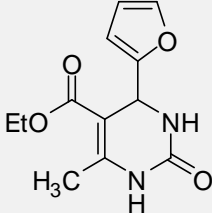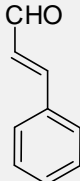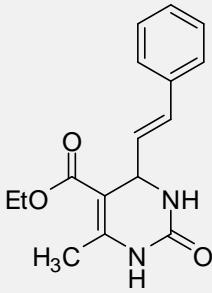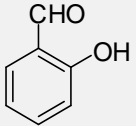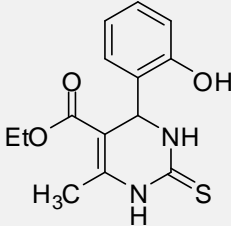
Several aromatic aldehydes (Table 1) carrying either electron releasing or electron withdrawing sustituents in the ortho, meta and para positions afforded high yields of the products. An important feature of this procedure is the survival of variety of functional groups such as ether, nitro groups, and halides under the reaction conditions. Thiourea also reacts under similar conditions to give their corresponding 3, 4-dihydropyrimido-2(1H)thiones. The proposed mechanism for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-one and thione derivatives in the glycerol media has been shown in Scheme 2.
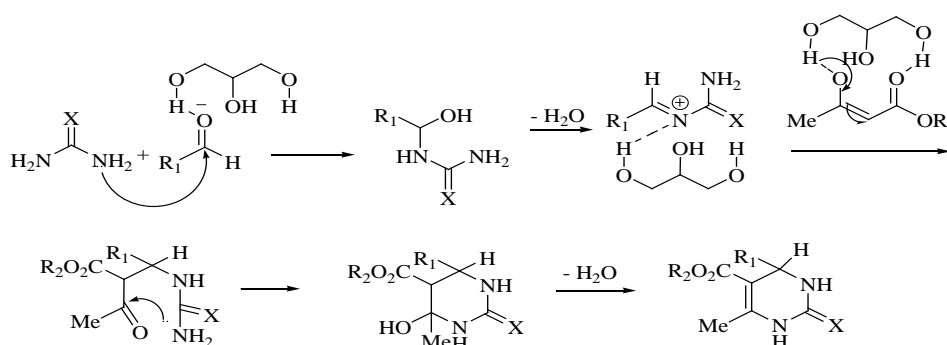
Scheme 2. Suggested mechanism for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-one/thiones.

Table 1. Synthesis of 3,4-dihydropyrimidin-2(1*H*)-one and thion derivatives in the presence of glycerol.

Entry	Aldehyde	X	Product	Time, h	Yield, %	M. P. °C Found; Reported[ref]
1		O		2.0	85	202-203 203-204[15]
2		O		1.0	80	224-227 225-227[15]
3		O		3.5	70	254-257 257-259[15]
4		O		3.0	65	203-205 206-208[16]
5		O		1.0	68	237-240 240-242[16]
6		S		1.0	35	237-239 240-241[17]

Entry	Aldehyde		Product	Time	Yield	mp (°C)
7	4-(N(CH$_3$)$_2$)C$_6$H$_4$CHO	S	ethyl 4-(4-(dimethylamino)phenyl)-6-methyl-2-thioxo-DHPM-5-carboxylate	2.0	60	204-207 / 206-208[15]
8	3-NO$_2$C$_6$H$_4$CHO	S	ethyl 6-methyl-4-(3-nitrophenyl)-2-thioxo-DHPM-5-carboxylate	2.0	65	203-205 / 206-209[15]
9	furan-2-carbaldehyde	S	ethyl 4-(furan-2-yl)-6-methyl-2-thioxo-DHPM-5-carboxylate	1.5	30	180-182 / 185[16]

Table 2. Comparison of efficiency of various catalysts in synthesis of ethyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate.

Entry	Catalyst	Mol % / g mL^{-1}	Temp., °C	Time, h	Yield, %	Ref.
1	Cl$_3$CCOOH	20 %	70	0.33	93	[18]
2	Al(NO$_3$)$_3$.9H$_2$O	15 %	Reflux	9.0	70	[21]
3	Na$_2$SeO$_4$	0.05 g	80	1.5	70	[20]
4	[Btto][*p*-TSA]	5.0 %	90	0.5	92	[21]
5	Al$_2$O$_3$/CH$_3$SO$_3$H	0.1 g	60	0.58	92	[22]
6	*p*-NH$_2$C$_6$H$_4$SO$_3$H	0.01 g	100	0.83	90	[23]
7	Silica triflate	0.03 g	90	0.08	85	[24]
8	SiO$_2$-NPs	5.0 %	80	0.66	78	[25]
9	HClO$_4$-SiO$_2$	0.50 g	110	0.36	92	[26]
10	Co(NO$_3$)$_2$.6H$_2$O	15 %	80	0.23	93	[27]
11	Ce(NO$_3$)$_3$.6H$_2$O	5.0 %	80	0.41	89	[28]
12	SiO$_2$-Cl	2.5 %	80	3.0	91	[29]
13	Glycerol	1.0 mL	100	1.0	80	This work

In order to show the merit of the present work, we compared the results of the synthesis of ethyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Entry 1 in Table l) with some previously reported catalysts. The yield of product in the presence of glycerol is comparable to the reported catalysts. However, reaction in the presence of these catalysts required less catalyst than this work (Table 2).

CONCLUSION

In continuation of our earlier work, carried to develop convenient synthetic protocols for the synthesis of bioactive heterocycles[30-32] by employing green tools and considering the above urgent need to provide convenient rapid route for the DHPMs, here we report for the first time the Biginelli reaction by subjecting substituted quinoline methoxy benzaldehydes, ethyl acetoacetate, urea and thiourea in glycerol medium and catalyst for obtaining new DHPMs.

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COMPUTATION OF CHEMICAL POTENTIAL AND FERMI-DIRAC INTEGRALS APPLIED TO STUDY THE TRANSPORT PHENOMENA OF SEMICONDUCTORS

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In the given paper, two methods of calculating with high precision accuracy the chemical potential and the integrals of the type called the Fermi–Dirac of different indexes are presented. Our calculations are conclusive with already existing data. These data are essential not only in the study of the theory of solids but at the explanation of the experimental results of investigated transport phenomena in solids, namely, in semiconductors.

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Introduction

The physical laws of systems consisting of a huge number of particles are of a statistical nature. Statistical distribution determines the probability of having those or other defining states parameters of the particles of the system.[1] One example of systems of the huge number of particles that requires a statistical approach is the solid state, in particular, semiconductors. The distribution of electrons over energies, namely, the Fermi–Dirac distribution, is the most important. The Boltzmann distribution, which is valid for particles obeying classical mechanics, is the limiting case of the Fermi-Dirac distribution. In the state of statistical equilibrium, the ideal electrons gas in solid state obeys the Fermi–Dirac statistics.[2,3] Different physical phenomena are differently sensitive to the type of statistical distribution. When considering the transport properties in a solid state, we inevitably collide with integrals of the type called the Fermi–Dirac integrals.[2,3] These are certain integrals often encountered not only in the study of the theory of semiconductors but at the explanation of the experimental results of investigated transport phenomena in semiconductors.

In this case, we have to use not only the tables of values of the Fermi integral but also their approximate formulas.[4] However, the calculation of integrals according to approximate formulas and tables gives a sufficiently high value of error, especially for large and small values of the reduced Fermi level. The error can reach approximately 25%. Using approximations is inconvenient and inaccurate. Therefore, the goal of our paper is to find an appropriate method for calculation of the Fermi–Dirac integrals for application in the study of semiconductors properties with

high accuracy $\ll 1\%$. The presented paper allows also determining a normalization constant, included in the Fermi–Dirac statistics, - the chemical potential with high reasonable accuracy.

Methodology

Gauss–Legendre method integrals solution

Functional integral according to Gauss–Legendre method is presented as the sum of (*n-1*) coefficients:

$$I \approx C_0 f(x_0) + C_1 f(x_1) + C_2 f(x_2) + C_3 f(x_3) + ... + C_{n-1} f(x_{n-1})$$

(1)

Let's say, at searching of integral we foresee only 2 coefficients, then it follows from (1):

$$I \approx C_0 f(x_0) + C_1 f(x_1)$$ (2)

This expression consists of 4 unknown coefficients (C_0, C_1, x_0, x_1) and, consequently, we need 4 boundary conditions:

$$f = const \quad f = x \quad f = x^2 \qquad f = x^3$$ (3)

The value of integral may be taken at an arbitrary [*a,b*] boundary. In our case, we take [–1,1] interval and const=1. From (3), boundary conditions follow:

$$\int_{-1}^{1} 1 dx = C_0 f(x_0) + C_1 f(x_1) = 2$$

$$\int_{-1}^{1} x dx = C_0 f(x_0) + C_1 f(x_1) = 0$$

$$\int_{-1}^{1} x^2 dx = C_0 f(x_0) + C_1 f(x_1) = \frac{2}{3}$$

$$\int_{-1}^{1} x^3 dx = C_0 f(x_0) + C_1 f(x_1) = 0$$

(4)

The solution of (4) equations gives the following values for *C* and *x* coefficients:

$$C_0 = 1 \quad x_0 = -\frac{1}{\sqrt{3}}$$
$$C_1 = 1 \quad x_1 = \frac{1}{\sqrt{3}}$$
(5)

Taking into account the value of two coefficients, the magnitude of integral is:

$$I = f(-\frac{1}{\sqrt{3}}) + f(\frac{1}{\sqrt{3}})$$
(6)

Taking into account 4 coefficients, we have to add 4 boundary conditions: $f=x^4$, $f=x^5$, $f=x^6$, $f=x^7$. At these boundary conditions calculated coefficients are:

$$C_0 = \frac{18-\sqrt{30}}{36} \quad C_2 = \frac{18+\sqrt{30}}{36}$$
$$C_1 = \frac{18+\sqrt{30}}{36} \quad C_3 = \frac{18-\sqrt{30}}{36}$$
(7)

$$x_0 = -\frac{\sqrt{525+70\sqrt{30}}}{35} \quad x_2 = \frac{\sqrt{525-70\sqrt{30}}}{35}$$
$$x_1 = -\frac{\sqrt{525-70\sqrt{30}}}{35} \quad x_3 = \frac{\sqrt{525+70\sqrt{30}}}{35}$$

These coefficients are needed to be installed into (1) for calculation of the digital value of integral. If we take into account n coefficients, we will need $2n$ boundary conditions.

In general, our task is to solve integral

$$I = \int_a^b f(x)dx$$

in arbitrary boundaries. For calculation of integral, it is necessary to transfer the boundary [a,b] into [–1,1]. Let's say, the value of the new argument is given by:

$$x = a_1 + a_2 x_d$$
(8)

and we search the integral value in the form of

$$I = \int_{-1}^1 f(x_d)dx_d$$

because integrals values are equal to each other:

$$I = \int_{-1}^1 f(x_d)dx_d \quad = \quad I = \int_a^b f(x)dx$$

From this it follows new conditions:

$$a_1 + a_2 = b$$
$$a_1 - a_2 = a$$
$$\quad x = \frac{b+a}{2} + \frac{b-a}{2}x_d$$

$$dx = \frac{b-a}{2}dx_d$$

Finally, for integral solved with two coefficients we obtain formula:

$$. \quad \int_a^b f(x)dx = \int_{-1}^1 \frac{b-a}{2}f\left(\frac{a+b}{2} + \frac{b-a}{2}x_d\right)dx_d$$
(9)

The more terms we take into account in the formula (1), the more accurate value of integral will be. In general, taking into n coefficients:

$$\int_a^b f(x)dx = \sum_{i=1}^n C_i \frac{b-a}{2}f\left(\frac{a+b}{2} + \frac{b-a}{2}x_i\right)$$
(10)

where $f(x)$ is an arbitrary function, which is continuous in [a,b] interval and C_i and x_i are coefficients found from boundary conditions.

The second way to calculate C_i and x_i coefficients is to solve Legendre polynomial equitations:[5,6]

$$P_n(x_i) = 0$$
(11)

$$C_i = \frac{2(1-x_i^2)}{[nP_{n-1}(x_i)^2]}$$
(12)

To obtain C_i and x_i coefficients, first, we have to generate Legendre polynomials and solve them. We can use MATLAB-s built-in functions to generate polynomials and solve them[7] (legendrePolynomials_1.m), or we can manually generate. Program (legendrePolynomials_2.m) uses polynomials properties:[5]

$$P_0(x) = 1$$
$$P_1(x) = x$$
$$P_2(x) = \frac{1}{2}(3x^2 - 1)$$
$$P_3(x) = \frac{1}{2}(5x^3 - 3x)$$

,

$$P_{(n+1)} = \frac{2n+1}{n+1}xP_n(x) - \frac{n}{n+1}P_{n-1}(x)$$
(13)

These values are uploaded on the repository (roots_2, weights_2).[7]

Method of undefined integrals solution

Let's say the integral is not given in limited [a,b] interval, but in [0,+∞] range. We can decompose integral into two parts:

$$. \quad \int_0^\infty f(x)dx = \int_0^1 f(x)dx + \int_1^\infty f(x)dx$$
(14)

In the second part of integral, we substitute the variable:

$$t = \frac{1}{x} \quad dx = -\frac{1}{t^2}dt \quad \begin{matrix} x=1 & t=1 \\ x=\infty & t\approx 0 \end{matrix}$$

Finally, we obtain formula (15) for approximate calculation of integral:

$$\int_0^\infty f(x)dx = \int_0^1 f(x)dx + \int_0^1 \frac{1}{t^2} f\left(\frac{1}{t}\right)dt \qquad (15)$$

We can apply (10) formula to the two parts of this integral and solve any integral, which is defined in this range. Taking into account (14) and (15) formulas, we obtain:

$$\int_0^1 f(x)dx = \sum_{i=1}^n C_i 0.5 f(0.5 + 0.5x_i)$$

$$\int_0^1 \frac{1}{t} f\left(\frac{1}{t}\right)dt = \sum_{i=0}^n C_i 0.5 \frac{1}{0.5 + 0.5x_i} f\left(\frac{1}{0.5 + 0.5x_i}\right) \qquad (16)$$

Calculation of integrals by (16) formulas and their summation give the final meaning of (14) integral.

Integral Fermi and its derivative

The general view of integrals of Fermi is given by the formula:

$$F_{(k)}(\xi) = \frac{1}{\Gamma(k+1)} \int_0^\infty \frac{x^k dx}{e^{x-\xi}+1} \qquad (17)$$

where ξ is the chemical potential. Many authors do not take into account $\Gamma(k+1)$ member and introduce integral Fermi as:

$$F_{(k)}(\xi) = \int_0^\infty \frac{x^k dx}{e^{x-\xi}+1} \qquad (18)$$

The formula for Fermi integrals derivative is given by:

$$\frac{dF_{(k)}(\xi)}{d\xi} = F_{(k-1)}(\xi) \qquad (19)$$

For gamma function, given in (17) formula, it can be written:

$$\Gamma(n) = (n-1)!$$

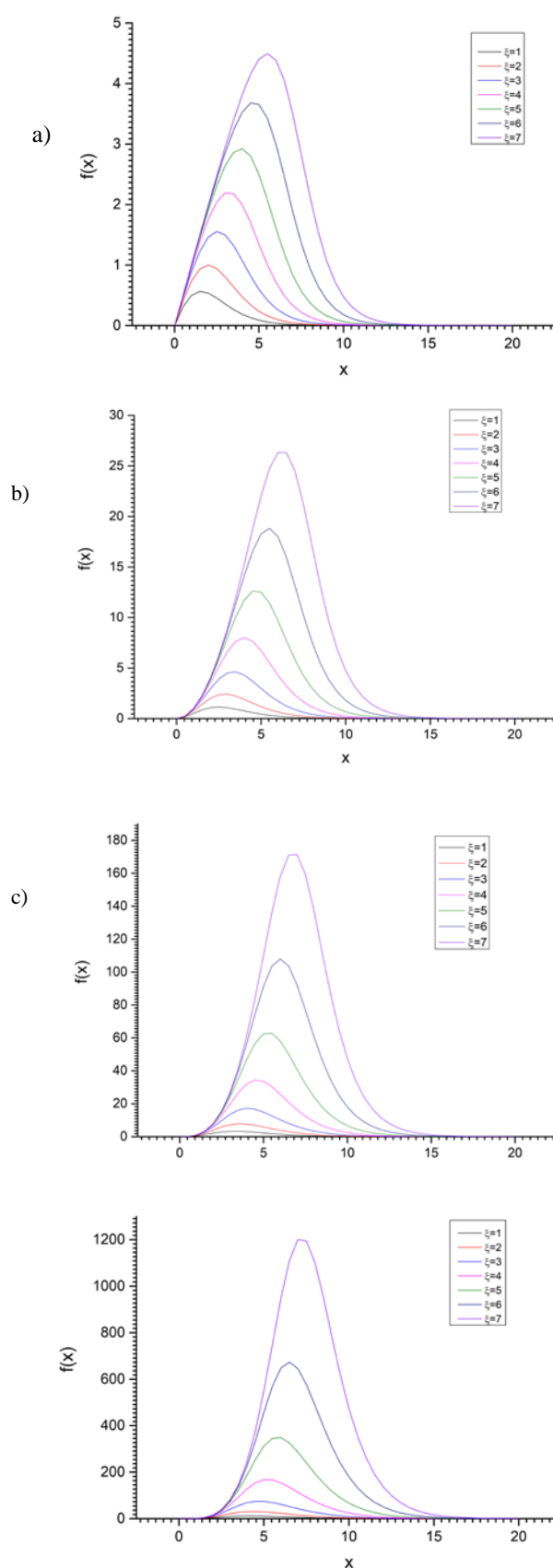If *n* is a natural number,

$$\Gamma(n+1) = n\Gamma(n)$$

It is also known, that

$$\Gamma\left(\frac{1}{2}\right) = \sqrt{\pi}$$

$$\Gamma\left(\frac{3}{2}\right) = \frac{\sqrt{\pi}}{2}$$

The graphics of integrand function in (18) formula for different values of *k* and ξ are given in Fig.1. It is clear from

Fig.1 that these functions are decomposable and it is possible to integrate them in certain approximation.

Figure 1. Dependence of integrand functions of Fermi integrals of different indexes (*k*) on *x* coefficient (parameter in Gauss–Legendre decomposition) for different values of chemical potential (ξ) according (18) formula.a) $k = 1$; b) $k = 2$; c) $k = 3$; d) $k = 4$

Table 1. Fermi integrals calculated using Gauss–Legendre numerical method for different k and ξ values.

ξ	$F_{(-0.5)}(\xi)$	$F_{(0)}(\xi)$	$F_{(0.5)}(\xi)$	$F_{(1)}(\xi)$	$F_{(1.5)}(\xi)$	$F_{(2)}(\xi)$	$F_{(2.5)}(\xi)$	$F_{(3)}(\xi)$	$F_{(3.5)}(\xi)$	$F_{(4)}(\xi)$
-10	0.000080	0.000045	0.000040	0.000045	0.000060	0.000091	0.000151	0.000272	0.000528	0.001090
-9.5	0.000132	0.000075	0.000066	0.000075	0.000100	0.000150	0.000249	0.000449	0.000871	0.001796
-9	0.000218	0.000123	0.000109	0.000123	0.000164	0.000247	0.000410	0.000740	0.001435	0.002962
-8.5	0.000359	0.000203	0.000180	0.000203	0.000270	0.000407	0.000676	0.001221	0.002367	0.004883
-8	0.000592	0.000335	0.000297	0.000335	0.000446	0.000671	0.001115	0.002013	0.003902	0.008051
-7.5	0.000975	0.000553	0.000490	0.000553	0.000735	0.001106	0.001838	0.003318	0.006433	0.013274
-7	0.001607	0.000911	0.000808	0.000912	0.001212	0.001824	0.003030	0.005471	0.010606	0.021884
-6.5	0.002649	0.001502	0.001332	0.001503	0.001998	0.003006	0.004996	0.009020	0.017486	0.036081
-6	0.004364	0.002476	0.002195	0.002477	0.003294	0.004956	0.008236	0.014870	0.028829	0.059485
-5.5	0.007188	0.004078	0.003617	0.004083	0.005429	0.008169	0.013577	0.024514	0.047527	0.098070
-5	0.011828	0.006715	0.005957	0.006727	0.008946	0.013465	0.022379	0.040410	0.078350	0.161676
-4.5	0.019442	0.011048	0.009807	0.011078	0.014739	0.022187	0.036883	0.066607	0.129153	0.266522
-4	0.031894	0.018150	0.016128	0.018232	0.024269	0.036548	0.060771	0.109768	0.212870	0.439322
-3.5	0.052154	0.029750	0.026480	0.029972	0.039930	0.060169	0.100090	0.180844	0.350780	0.724052
-3	0.084849	0.048587	0.043366	0.049180	0.065611	0.098963	0.164740	0.297801	0.577843	1.193037
-2.5	0.136919	0.078889	0.070724	0.080459	0.107580	0.162524	0.270855	0.490021	0.951367	1.965030
-2	0.218160	0.126927	0.114587	0.131012	0.175800	0.266264	0.444552	0.805316	1.564959	3.234531
-1.5	0.341047	0.201412	0.183801	0.211781	0.285771	0.434565	0.727643	1.320874	2.570653	5.318800
-1	0.518823	0.313260	0.290500	0.338646	0.460847	0.705127	1.185963	2.159830	4.213244	8.732095
-0.5	0.761071	0.474075	0.449791	0.533215	0.734656	1.134363	1.920729	3.515183	6.881824	14.300130
0	1.067828	0.693144	0.678091	0.822463	1.152798	1.803077	3.082572	5.682171	11.183664	23.330758
0.5	1.426306	0.974072	0.990205	1.236711	1.772785	2.820956	4.886692	9.098479	18.043955	37.857518
1	1.814084	1.313255	1.396369	1.806278	2.661670	4.328312	7.626501	14.389290	28.831181	60.969145
1.5	2.207291	1.701405	1.900824	2.558140	3.891958	6.494340	11.683107	22.412341	45.503037	97.230062
2	2.587770	2.126918	2.502446	3.513905	5.537229	9.512626	17.529341	34.298126	70.764217	153.186814
2.5	2.945461	2.578877	3.196584	4.689454	7.668770	13.595469	25.728853	51.482272	108.226761	237.947389
3	3.276968	3.048573	3.976967	6.095726	10.353670	18.968485	36.931900	75.729458	162.565639	363.816745
3.5	3.582928	3.529734	4.837044	7.739928	13.654142	25.866260	51.869575	109.149979	239.665390	546.972565
4	3.865848	4.018131	5.770701	9.626660	17.627625	34.529198	71.347717	154.210694	346.756231	808.168220
4.5	4.128776	4.511027	6.772544	11.758804	22.327231	45.201382	96.241199	213.742039	492.539785	1173.453445
5	4.374651	5.006692	7.837941	14.138143	27.802316	58.129185	127.488879	290.942425	687.305373	1674.906250
5.5	4.606044	5.504053	8.962954	16.765772	34.099026	73.560391	166.089248	389.380971	943.038083	2351.371837
6	4.825101	6.002447	10.144236	19.642358	41.260784	91.743648	213.096735	512.999179	1273.519828	3249.205875
6.5	5.033577	6.501470	11.378929	22.768310	49.328692	112.928137	269.618566	666.111973	1694.424439	4423.020466
7	5.232895	7.000876	12.664570	26.143874	58.341866	137.363360	336.812082	853.408342	2223.407698	5936.431785
7.5	5.424209	7.500513	13.999019	29.769204	68.337698	165.299026	415.882435	1079.951738	2880.192997	7862.808723
8	5.608459	8.000292	15.380397	33.644392	79.352082	196.984965	508.080574	1351.180315	3686.653190	10286.021973
8.5	5.786419	8.500157	16.807039	37.769497	91.419585	232.671085	614.701470	1672.907025	4666.888990	13301.193045
9	5.958728	9.000074	18.277454	42.144555	104.573587	272.607329	737.082509	2051.319588	5847.304234	17015.442795
9.5	6.125925	9.500023	19.790299	46.769583	118.846403	317.043638	876.602036	2492.980354	7256.678336	21548.639382
10	6.288463	9.999991	21.344352	51.644591	134.269371	366.229930	1034.678067	3004.826267	8926.236815	27034.147723
10.5	6.446730	10.499971	22.938496	56.769577	150.872948	420.416105	1212.767150	3594.168865	10889.719696	33619.578292
11	6.601061	10.999955	24.571701	62.144532	168.686770	479.852017	1412.363326	4268.694535	13183.449811	41467.545021
11.5	6.751748	11.499944	26.243030	67.769486	187.739872	544.787974	1634.998693	5036.469111	15846.411090	50756.452690
12	6.899048	11.999932	27.951588	73.644384	208.060299	615.473181	1882.237194	5905.919849	18920.251812	61681.049761
12.5	7.043184	12.499917	29.696558	79.769248	229.675833	692.158493	2155.684591	6885.876865	22449.502262	74453.755063
13	7.184368	12.999931	31.477293	86.144477	252.614812	775.098142	2456.990127	7985.568418	26481.571170	89305.014338
13.5	7.322766	13.499917	33.292849	92.769192	276.900355	864.529451	2787.775804	9214.382245	31066.001979	106481.391495
14	7.458527	13.999844	35.142482	99.643325	302.558861	960.706699	3149.769214	10582.385598	36256.535226	126253.971250
14.5	7.591864	14.499956	37.026477	106.770282	329.628301	1063.925362	3544.868194	12100.472868	42111.352067	148918.432812
15	7.722883	15.000121	38.943590	114.147113	358.120538	1174.378450	3974.595997	13778.315868	48685.456412	174767.250174
15.5	7.851551	15.499752	40.891069	121.765761	388.030742	1292.210038	4440.373101	15625.664267	56036.688211	204116.965869
16	7.978094	15.999386	42.870763	129.636690	419.428203	1417.862657	4944.839304	17657.354518	64244.638244	237379.517106
16.5	8.102938	16.500262	44.886890	137.777816	452.403877	1551.835529	5490.763439	19888.479776	73389.579386	274971.640142
17	8.225953	17.001340	46.934200	146.167673	486.885544	1693.957680	6078.195623	22323.282631	83509.382081	317148.914595
17.5	8.346576	17.499994	49.001676	154.764116	522.728902	1843.819144	6706.467018	24964.288331	94640.747025	364190.295690
18	8.465035	17.997093	51.093520	163.590796	560.072948	2002.228306	7380.152559	27836.647899	106918.386825	416801.505870
18.5	8.582563	18.497577	53.230315	172.736759	599.316143	2171.018229	8107.863355	30981.410198	120539.839988	475938.428659
19	8.699711	19.003177	55.417601	182.221026	640.533573	2350.541470	8891.492840	34409.422944	135568.153097	541963.950641
19.5	8.815135	19.507480	57.625903	191.912223	683.155636	2538.395308	9721.205939	38081.863815	151857.364686	614368.443194
20	8.927052	20.002597	59.821192	201.667330	726.598591	2732.281123	10588.381355	41968.724103	169316.409651	692959.229516
20.5	9.035835	20.490508	62.014455	211.548266	771.210166	2934.130082	11503.598132	46127.163845	188250.202101	779344.274730
21	9.144327	20.984056	64.264387	221.825881	818.251380	3149.859592	12494.815952	50690.082514	209293.696928	876570.581204
21.5	9.255096	21.494325	66.619219	232.712178	868.664160	3383.702824	13581.288777	55746.134990	232860.143722	986587.644347
22	9.367376	22.016786	69.054145	244.077558	921.793834	3632.438102	14747.505621	61222.093445	258610.281543	1107853.781600
22.5	9.477076	22.531761	71.475319	255.478027	975.555760	3886.350156	15948.528937	66911.728985	285605.661762	1236138.584063
23	9.580333	23.021253	73.799663	266.533674	1028.230269	4137.743722	17150.381409	72667.432314	313218.016810	1368839.633026
23.5	9.677238	23.486424	76.036815	277.313023	1080.265921	4389.406492	18369.776040	78586.789805	342005.732957	1509101.370114
24	9.772329	23.949657	78.297661	288.367539	1134.414867	4655.115422	19675.865035	85017.732716	373723.077942	1665785.362059
24.5	9.871685	24.440360	80.724949	300.392328	1194.072448	4951.506346	21150.402315	92363.210432	410361.858345	1848765.243487
25	9.978684	24.974206	83.391576	313.727459	1260.830453	5286.059615	22828.702401	100790.828387	452722.379407	2061888.667774
25.5	10.091017	25.538479	86.228622	328.004250	1332.737838	5648.543680	24657.529991	110025.528551	499392.470545	2297948.317296
26	10.201425	26.095944	89.045751	342.252668	1404.865112	6013.977515	26510.633196	119430.968104	547173.548812	2540911.531003
26.5	10.302280	26.608051	91.648688	355.496500	1472.321179	6357.929723	28266.366977	128403.557665	593081.912366	2776090.276727
27	10.390462	27.059599	93.964039	367.385216	1533.454004	6672.741724	29889.976731	136790.079311	636469.753387	3000921.095439
27.5	10.468938	27.466702	96.079651	378.399049	1590.894336	6972.848921	31460.775056	145026.735497	679737.892201	3228625.177457
28	10.545059	27.868165	98.200806	389.626352	1650.424856	7289.039459	33143.006230	153991.352743	727586.347713	3484409.762379
28.5	10.627588	28.310113	100.570847	402.353554	1718.859757	7657.477976	35128.967815	164708.313287	785481.846607	3797499.424296

29	10.723418	28.828660	103.379363	417.578079	1801.457447	8105.944774	37565.730293	177957.836926	857572.092172	4189989.132597
29.5	10.834220	29.431761	106.663945	435.476104	1899.035693	8638.191699	40470.262904	193815.317953	944184.493311	4663258.212882
30	10.954374	30.087872	110.248115	455.062998	2006.114497	9223.788410	43673.935454	211348.075056	1040169.670945	5188924.669727

Finally, the Fermi integrals values have been calculated by the Gauss–Legendre method, where C_i and x_i coefficients have been found from (11) and (12) formulas. The Program has been written in Matlab programming language (Fermi_integral_calculator_1.m) and it uses 100 points of Gauss–Legendre coefficients.[7] The values of calculated Fermi integrals for different parameters k and ξ are given in Table 1.

Simson's integral calculation method

Another way to calculate integrals of function $f(x)$, which are defined in $[a,b]$ range, is Simson's integration method, the general formula of which is given in (20):[7]

$$\int_a^b f(x)dx = \frac{\Delta x}{3}(f(a)+f(b)+4(f(x_1)+f(x_3)+.....$$

$$f(x_5)+f(x_{2n+1}))+2(f(x_2)+.....$$

$$f(x_4)+f(x_6)+...f(x_{2n})))$$

$$\Delta x = \frac{b-a}{n} \qquad (20)$$

$$\int_a^b f(x)dx = \frac{\Delta x}{3}(\text{First}+\text{Last}+4(\text{sum of odds})+2(\text{sum of evens}))$$

Results for Simson's rule are in good agreement with the Gauss–Legendre method.

Error estimation

Finally, we show the advantages of the method presented in the article by calculating the error of implemented calculations.

Gauss–Legendre method error estimation has been done by using (21) formula:

$$\text{Error} = Ef^{(2n)}(\theta) \qquad (21)$$

where

$$E = \frac{2^{(2n+1)}(n!)^4}{(2n+1)((2n)!)^3} \qquad (22)$$

and $a \leq \theta \leq b$.

The values of E parameter estimated by (22) formula are given for different n in Table 2.

Table 2. Values of E according to (22) formula for different n

n	E	n	E
2	0.00741	16	2.73804E-45
3	6.34921E-5	17	6.10607E-49
4	2.87946E-7	18	1.21246E-52
5	8.07929E-10	19	2.15736E-56
6	1.54087E-12	20	3.45947E-60
7	2.12743E-15	21	5.0253E-64
8	2.22477E-18	22	6.64363E-68
9	1.82325E-21	23	8.02751E-72
10	1.20251E-24	24	8.89959E-76
11	6.52056E-28	25	9.08485E-80
12	2.95829E-31	26	8.56732E-84
13	1.13949E-34	27	7.48625E-88
14	3.77297E-38	28	6.07844E-92
15	1.08539E-41	29	4.59789E-96
16	2.73804E-45	30	3.248E-100

It is clear that the increase of n-value decreases the value of E and error goes to nearly zero.

Conclusion

The chemical potential and Fermi–Dirac integrals are essential for a basic understanding of semiconductors properties. In this paper, there have been calculated Fermi–Dirac integrals by two different ways – Gauss–Legendre and Simson's methods. Both methods are in good agreement with each other. Our data let reduce the error of calculation of Fermi–Dirac integrals up to <<1%.

Acknowledgment

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SILICA SUPPORTED PERCHLORIC ACID: AN EFFICIENT AND RECYCLABLE CATALYST FOR SYNTHESIS OF BENZIMIDAZOLO[2,3-*b*]QUINAZOLINONES

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Keywords: 2-Aminobenzimidazole; benzimidazolo[2,3-*b*]quinazolinones; heterogeneous catalyst; perchloric acid; silica.

Synthesis of benzimidazolo[2,3-*b*]quinazolinone derivatives has been reported in excellent yields by using silica-supported perchloric acid (HClO₄-SiO₂) as a mild and reusable heterogeneous catalyst. The procedure is simple, environmentally benign and has the advantage of high atom economy. Furthermore, the catalyst can be recovered and reused several times efficiently without substantial loss of catalytic activity.

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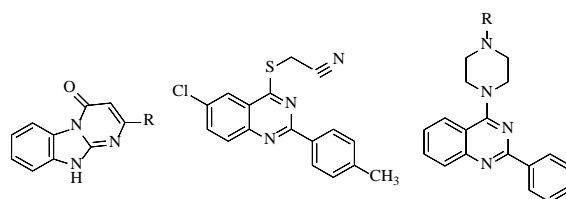
Figure 1. Biologically important quinazolines

INTRODUCTION

Heterogeneous catalysis is an interesting area of research from an industrial point of view. It has the advantages of thermal stability, high selectivity, better activity, ease of separation, recyclability and long life.[1-4] Solid acid catalysts play an important role in organic transformations due to many advantages such as simplicity in handling, decreased reactor corrosion problems and more environmentally safe disposal of the catalyst.[5-7] Quinazolinones and their derivatives have been reported to possess interesting pharmacological activities, such as antibacterial,[8-9] antihypertension,[10] antihistaminic,[11] analgesic, anti-inflammatory,[12] anticancer,[13] and anti-HIV.[14] Moreover, a variety of quinazolinones derivatives with different biological activities were synthesized by medicinal chemistry researchers. These derivatives also have a long history of applications in agrochemicals and the pharmaceutical industry as herbicides and active pharmaceuticals. Awareness about environmental hazards in chemical industries becomes a significant concern due to the generation of waste products that leads to the development of environment-friendly synthetic processes. Heterocyclic compounds constitute comprehensive examples in pharmaceutical and chemical industries. Because of their potent physiological properties, they resulted in numerous applications.[15]

Several methods have been reported for the synthesis of substituted benzimidazolo-quinazolinones. The most common method is the reaction of substituted aldehydes with 2-aminobenzimidazole and dimedone using various basic and acidic catalysts under reflux conditions,[15-16] ionic liquids[17] and heteropolyacids.[18]

All these methods are associated with several limitations such as the use of metal catalysts, harsh reaction conditions, tedious experimental procedure, low yields, prolonged reaction time and use of costly and moisture-sensitive catalyst. Hence, there is a need to develop a rapid, efficient and environmentally benign synthetic procedure for the synthesis of benzimidazole[2,3-*b*]quinazolinone derivatives.

In continuation of previous studies on silica-supported perchloric acid[19-21] herein, we developed an efficient and environment-friendly method for the synthesis of quinazolinone derivatives by the condensation of substituted aldehydes, 2-aminobenzimidazole, and dimedone using silica-supported perchloric acid as a heterogeneous catalyst (Scheme 1).
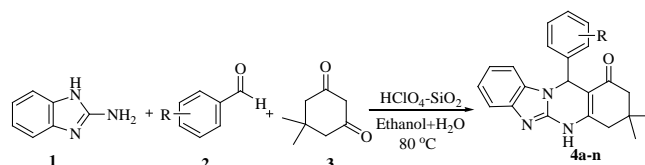
Scheme 1. Synthesis of benzimidazolo[2,3-*b*]quinazolinones

EXPERIMENTAL

Preparation of HClO₄-SiO₂ catalyst:

Aqueous perchloric acid (70 %, 1.8g, 12.5 mmol) was added to a suspension of SiO₂ (230-400 mesh, 23.7 g) in

ether (70 ml). The mixture was concentrated and the residue was heated at 100 °C for 72 h under vacuum to give HClO₄-SiO₂ (0.5 mmol g⁻¹) as free-flowing powder.[22]

General procedure: synthesis of 3,3-dimethyl-12-phenyl-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-1(2*H*)-one

Silica supported perchloric acid (10 wt.%) was added to a mixture of 2-aminobenzimidazole (1 mmol), aldehyde (1 mmol) and dimedone (1) mmol in 1:1 ethanol: water (5 mL). The reaction mixture was stirred at 80 °C for 20-40 minutes. After completion of the reaction, as monitored by TLC, the reaction mass was filtered. The filtrate was heated to remove the solvent. Separated solid was washed with water and dried under reduced pressure. Furthermore, the separated catalyst was dried and reused.

Similarly, the other derivatives were also synthesized using the same method (Table 1). Spectral data of the synthesized compounds is mentioned below:

3,3-Dimethyl-12-phenyl-1,2,3,4,5,12-hexahydrobenzo[4,5]-imidazo[2,1-*b*]quinazolin-1-one (4a)

M.p. 270-280 °C; IR (KBr): 3350, 2920, 1640, 1620, 1610,1565 cm⁻¹; ¹H-NMR (DMSO-d_6, 300 MHz): δH= 1.06 (s, 3H, CH₃), 1.09 (s, 3H, CH₃), 2.04 (s, 2H, CH₂), 2.30 (s, 2H, CH₂), 6.41 (s, 1H, CH), 6.93-7.38 (m, 9H, Ar-H), 11.12 (s, 1H, NH) ppm.

3,3-Dimethyl-12-(2,4-dichlorophenyl)-1,2,3,4,5,12-hexahydro-benzo[4,5]imidazo[2,1-*b*]quinazolin-1-one (4b)

M.p. 315-330 °C; IR (KBr): 3085, 2930, 1615, 1520 cm⁻¹; ¹H-NMR (DMSO-d_6, 300 MHz): δ H = 1.0 (s, 3H, CH₃), 1.08 (s, 3H, CH₃), 2.19 (s, 2H, CH₂), 2.35 (s, 2H, CH₂), 6.90 (s, 1H, CH), 7.25-8.10 (m, 4H, Ar-H), 7.25-8.10 (m, 2H, Ar-H), 8.15 (s, 1H, Ar-H), 911.31 (s, 1H, NH) ppm.

3,3-Dimethyl-12-(4-bromophenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-1-one (4c)

M.p. 295-300 °C; IR (KBr): 3420, 2920, 1640, 1610, 1530 cm⁻¹; ¹H NMR (DMSO-d_6, 300 MHz): δ H = 0.90 (s,3H, CH₃), 1.05 (s, 3H, CH₃), 2.00 (s, 2H, CH₂), 2.20 (s, 2H, CH₂), 6.42 (s,1H, CH), 6.98-7.88 (m, 8H, Ar-H), 11.00 (s, 1H, NH) ppm.

3,3-Dimethyl-12-(4-nitrophenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-1-one (4d)

M.p. 290-300 °C; IR (KBr): 2869, 1681, 1612, 1518 cm⁻¹; ¹H-NMR (DMSO-d_6, 300 MHz): δ H = 0.85 (s,3H, CH₃), 1.6 (s, 3H, CH₃), 2.20 (s, 2H, CH₂), 2.28 (s, 2H, CH₂), 6.60 (s, 1H, CH), 7.04-810 (m, 8H, Ar-H), 11.90 (s, 1H, NH) ppm.

3,3-Dimethyl-12-(4-flurophenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-1-one (4e)

M.p.285-295 °C; IR (KBr): 3020, 2915, 1645, 1580, 1330 cm⁻¹; ¹H NMR (DMSO-d_6, 300 MHz): δ H=1.04 (s,3H, CH₃), 1.07 (s, 3H, CH₃), 2.20 (s, 2H, CH₂), 2.04 (s, 2H, CH₂), 6.49 (s, 1H,CH), 6.90-7.90 (m, 8H, Ar-H), 10.90 (s, 1H, NH) ppm.

3,3-Dimethyl-12-(4-chlorophenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo [2,1-*b*]quinazolin-1-one (4f)

M.p. 285-295 °C; IR (KBr): v_{max} = 3465, 2945, 1670, 1619, 1560, 1566 cm⁻¹; ¹H NMR (DMSO-d_6, 300 MHz): δ H = 1.06 (s,3H, CH₃), 1.11 (s, 3H, CH₃), 2.03 (s, 2H, CH₂), 2.40 (s, 2H, CH₂), 6.56 (s, 1H, CH), 6.94-7.53 (m, 8H, Ar-H), 11.27 (s, 1H, NH) ppm**.**

3,3-Dimethyl-12-(2,4,6-methoxyphenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-1-one (4g)

M.p. 292-302 °C; IR (KBr): 3210, 2969, 1690, 1590, 1312, 1258 cm⁻¹; ¹H-NMR (DMSO-d_6, 300 MHz): δ H = 1.09 (s, 3H, CH₃), 1.16 (s, 3H, CH₃), 2.11 (s, 2H, CH₂), 2.49 (s, 2H, CH₂), 3.69 (s, 3H, OCH₃), 3.75 (s, 6H, OCH₃), 6.30 (s, 1H, CH), 6.55 (s, 2H, Ar-H), 6.73-7.42 (m,4H, Ar-H), 11.01 (s, 1H, NH) ppm.

3,3-Dimethyl-12-(4-methoxyphenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-1-one (4h)

M.p. 280-290 °C; IR (KBr): 3243, 2961, 1680, 1641, 1612, 1589, 1566, 1258 cm⁻¹; ¹H NMR (DMSO-d_6, 300 MHz): δ H =1.03 (s, 3H, CH₃), 1.06 (s, 3H, CH₃), 2.06-2.15 (m, 2H, CH₂), 2.25-250 (m, 2H, CH₂), 3.66 (s, 3H, OCH₃), 6.35 (s, 1H, H-12), 6.73-7.42 (m, 8H, Ar-H), 11.01 (s, 1H, NH) ppm.

3,3-Dimethyl-12-(2,4-methoxyphenyl)-1,2,3,4,5,12-hexa-hydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-1-one (4i)

M.p. 250-260 °C; IR (KBr): 3085, 2925, 1600, 1575 1262 cm⁻¹; ¹H-NMR (DMSO-d_6, 300 MHz): δ H =1.06 (s, 3H, CH₃), 1.11 (s, 3H, CH₃), 1.90 (s, 2H, CH₂), 2.45 (s 2H, CH₂), 3.72 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 6.20 (s, 1H, CH), 6.54-7.44 (m, 3H, Ar-H), 6.58 (t, 1H, Ar-H), 7.44 (d, 1H, Ar-H), 7.00-7.50 (m, 4H, Ar-H), 11.21 (s, 1H, NH) ppm.

3,3-Dimethyl-12-(4-hydroxyphenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-1-one (4j)
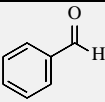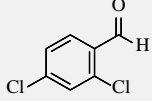
M.p. 270-275 °C; IR (KBr): 3469, 2962, 1574, 1264 cm⁻¹; ¹H-NMR (DMSO-d_6, 300 MHz):δ H = 1.06 (s, 3H, CH₃), 1.06 (s, 3H, CH₃), 2.04 (s, 2H, CH₂), 2.43 (s, 2H, CH₂), 6.19 (s, 1H, CH), 6.60-7.35 (m, 8H, Ar-H), 8-9.32 (s, 1H, OH), 11.01 (s, 1H, NH) ppm.

3,3-Dimethyl-12-(3-hydroxyphenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-1-one (4k)

M.p.287-292 °C; IR (KBr): 3090, 2950, 1572, 1249 cm⁻¹; ¹H-NMR (DMSO-d_6, 300 MHz): δ H =1.07 (s, 3H, CH₃), 1.09 (s, 3H, CH₃), 1.95 (s, 2H, CH₂), 2.50 (s, 2H, CH₂), 6.23 (s, 1H, CH), 6.69-7.00 (m, 3H, Ar–H), 7.10 (t, J = 7.90, Hz, 1H, Ar-H), 7.52 (d, J = 5.69, Hz, 1H, Ar-H), 7.30-7.70 (m, 4H, Ar-H), 9.20 (s, 1H, OH), 11.30 (s, 1H, NH) ppm.

3,3-Dimethyl-12-(4-methylphenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-1-one (4l)

M.p. 260-270 °C; IR (KBr): 3085, 2930, 1570, 1253 cm⁻¹; ¹H-NMR (DMSO-d_6, 300 MHz):δ H = 1.10 (s,3H, CH₃), 1.12 (s, 3H, CH₃), 2.15 (s, 2H, CH₂), 2.40 (s, 2H, CH₂), 2.70 (s, 3H, CH₃), 6.35(s, 1H, H-12), 6.60-7.35 (m, 8H, Ar-H), 11.01 (s, 1H, NH) ppm.

3,3-Dimethyl-12-(2-nitrophenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-1-one (4m)

M.p.275-280 °C; IR (KBr): 3400, 2995, 1589, 1320 1258, 749 cm⁻¹; ¹H NMR (DMSO-d_6, 300 MHz): δ H = 1.07 (s, 3H, CH₃), 1.11 (s, 3H, CH₃), 2.19 (s, 2H, CH₂), 2.70 (s, 2H, CH₂), 6.45 (s, 1H, CH), 7.05 (d, 1H, Ar-H), 7.20-7.35 (m, 1H, Ar-H), 7.15-7.44 (m, 1H, Ar-H), 7.15-7.44 (m, 1H, Ar-H), 7.44 (d, J = 8.15 Hz, 1H, Ar-H), 7.50-7.90 (m, 4H, Ar-H), 11.29 (s, 1H, NH) ppm.

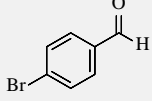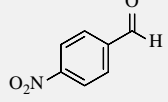**3,3-Dimethyl-12-(2-methoxyphenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-1-one (4n)**
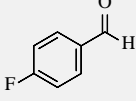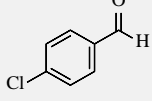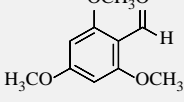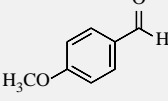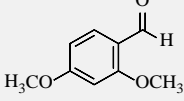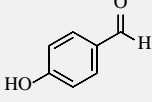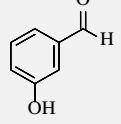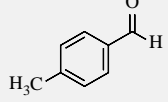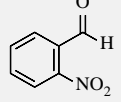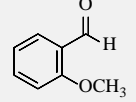
M.p. 245-255 °C; IR (KBr): 3089, 2895, 1590, 1248, 740 cm⁻¹; ¹H-NMR (DMSO-d_6, 300 MHz): δH=1.09 (s,3H, CH₃), 1.14 (s, 3H, CH₃), 1.99 (s, 2H, CH₂), 2.45 (s, 2H, CH₂), 3.72 (s, 3H, OCH₃), 6.29 (s, 1H, CH), 6.90-7.44 (m, 4H, Ar-H), 7.15-7.64 (m, 4H, Ar-H), 11.27 (s, 1H, NH) ppm.

RESULTS AND DISCUSSION

We developed a new method for the synthesis of benzimidazolo[2,3-*b*]quinazolinone derivatives in good yields by using HClO₄-SiO₂ as a mild and reusable heterogeneous catalyst in water:ethanol (1:1) solvent. The procedure is environment-friendly, operationally simple and thus has the advantage of high atom economy. Furthermore, the catalyst can be recovered and reused several times efficiently without substantial loss of activity. We also studied the reaction in aqueous medium only, but the reaction proceeded very slowly and the product formation was also very poor. When we used ethanol:water (1:1) solvent system, the reaction proceeded faster with a high yield of the corresponding product.

The effect of temperature on yield of the product **4a** was studied by carrying the reactions at different temperatures (30, 55, 80 and 100 ºC) as shown in Table 2. By raising the reaction temperature from room temperature to 100 ºC gradually, the yield of reactions was found to be increased.

Table 1. Synthesis of 3,3-dimethyl-12-(un)substituted phenyl-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-1(2*H*)-ones using silica supported perchloric acid.

Entry	Aldehydes (2)	Products (4)	Time (min)	Yield (%)
1		**4a**	30	85
2		**4b**	30	90
3		**4c**	40	85
4		**4d**	20	80
5		**4e**	25	75
6		**4f**	25	90
7		**4g**	30	80
8		**4h**	20	90
9		**4i**	25	90
10		**4j**	35	75
11		**4k**	30	90
12		**4l**	20	90
13		**4m**	25	90
14		**4n**	20	90

Reaction conditions: Aldehyde (1.0 mmol), dimedone (1.0 mmol), 2-aminobenzimidazole (1.0 mmol), HClO₄–SiO₂ (10 wt%) 20-40 min reflux.

At 80 °C temperature, the reaction completed in 25 minutes affording 90 % of product yield. Similarly, increasing the reaction temperature to 100 ºC does not affect the yield of the product significantly. Thus, we confirmed that 80 ºC was the optimum temperature for the transformation. Under these optimized conditions, various aldehydes were reacted with dimedone and aminobenzimidazoles, whose results are summarized in Table 1.

Table 2. Effect of temperature on the preparation of 3,3-dimethyl-12-phenyl-1,2,3,4,5,12-hexahydrobenzo[4,5]-imidazo[2,1-*b*]quinazolin-1-one (**4a**)

Entry	Temp., ºC	Time, min	Yield, %[@]
1	30	240	40
2	50	60	70
3	80	25	90
4	100	25	90

[@]Reactions performed in case of 4-chlorobenzaldehyde

Reusability of the catalyst

Solid silica-based perchloric acid works under heterogeneous conditions. It is an inexpensive and non-hazardous solid acid catalyst which can be easily handled and separated from the reaction mixture by simple filtration. The recovered catalyst was reused thrice for consecutive runs with a minimum variation of yields of the products. After completion of the reaction, the catalyst was filtered, thoroughly washed with ethanol and dried at 100 ºC for 2 hr and reused for subsequent runs (Table 3). This reusability demonstrates the high stability and turnover of solid silica-based perchloric acid under operating conditions.

Table 3.-Reusability of catalyst for the synthesis of 3,3-dimethyl-12-phenyl-1,2,3,4,5,12-hexahydrobenzo[4,5]-imidazo[2,1-*b*]quinazolin-1-one (**4a**)

Entry	Number of recycling□	Time, min	Yield, %[@]
1	Fresh	40	90
2	First	45	88
3	Second time	60	88
4	Third time	70	85

[@]Yields in case of 4-chlorobenzaldehyde

CONCLUSION

A convenient method has been developed by the reaction of 2-aminobenzimidazole, dimedone and aldehyde catalyzed by the silica-supported perchloric acid catalyst. Use of inexpensive and reusable catalyst, enhanced reaction rates, readily available starting materials, high yield and easy purification of the products are the key features of this method.

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ONE-POT SYNTHESES OF 2-(1*H*-BENZO[*d*]OXAZOLE-2-YL)-*N*-ARYLBENZAMIDES BY SELF-CATALYSIS

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A novel, efficient, and high-yielding one-pot three-component method was developed for the synthesis of 2-(1*H*-benzo[*d*]oxazole-2-yl)-N-arylbenzamides by combining phthaldichloride with anilines & o-aminophenol in water without any external catalyst. The environmentally friendly procedure, easy operation and mild reaction conditions enable the tolerance of a wide scope of functionalities as well as high reaction efficiency.

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INTRODUCTION

In today's world, the development of efficient, economical and environmentally friendly synthesis is an important challenge in modern organic syntheses.[1] In many synthetic organic processes, solvents represent a severe pollution problem. Thus, the replacement of hazardous solvents with relatively green solvents or the altogether elimination of use of hazardous solvents in chemical processes has been one of the key achievements of green chemistry.[2] Based on the principles of green chemistry, a green solvent should meet numerous criteria such as low toxicity, non-volatility, non-mutagenicity, non-flammability and widespread availability among others.[3] In the past decade, water,[4] glycerol,[5] polyethylene glycol,[6] ionic liquids have been used as green solvents in organic reactions. Among all the green solvents, water is the safest, cheapest and non-toxic solvent.[8] As a result, serious efforts are being made to develop water as a solvent for most of the organic syntheses and processes wherever possible.

Benzoxazoles are important building blocks in medicinal chemistry and can be found in a number of drug candidates under investigation for the treatment of various diseases.[8] The classical approach for the synthesis of benzoxazoles involves coupling of carboxylic acids with *o*-aminophenols by dehydration catalysed by acids.[8] However, the utility and applicability of this protocol is often compromised since it is usually run in volatile organic solvents and requires stoichiometric or excess corrosive and toxic oxidants such as DDC (dicyclohexyl carbodiimide), HgO , NiO$_2$, AgNO$_3$, KO$_2$ or H$_2$O$_2$/LiOH.[8]

Keeping the above results in mind, we now wish to report a synthesis of 2-(1*H*-benzo[*d*]oxazol-2-yl)-N-arylbenz-amides by combining phthaldichloride with anilines and *o*-aminophenol in water without any external catalyst at 100 °C for 60-90 min.

EXPERIMENTAL

^{1}H and ^{13}C-NMR spectra were recorded in DMSO-d_6 at 400 MHz and 100 MHz respectively. Chemical shifts (δ) are reported parts per million (ppm) and are referenced to tetramethylsilane (TMS) as internal standard. NMR multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad signal. The yields are based on isolated compounds after purification. Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC was run on silica gel-G and visualization was done using iodine or UV light. IR spectra were recorded using Perkin-Elmer 1000 instrument in KBr pellets. Mass spectra were recorded on Agilent-LCMS instrument under CI conditions and given by Q+1 values only. Starting materials phthaldichloride and substituted anilines were obtained from commercial sources and were used as such.

General procedure for preparation of 2-(1*H*-benzo[*d*]oxazole-2-yl)-N-arylbenzamides by one-pot synthesis

A mixture of phthaldichloride (**1**) (10 mM), substituted anilines (**2a-2h**) (10 mM), *o*-phenylenediamine (**3**) (10 mM), and water (30 mL) was heated at 100 °C for 60-90 min. At the end of this period, a colourless solid separated out from reaction mixture which was collected by filtration. The isolated solid was washed with water (20 mL) and dried. The product was recrystallized from ethanol solvent to obtain 2-(1*H*-benzo[*d*]oxazole-2-yl)-N-arylbenzamide (**4a-4h**).

2-(1*H*-Benzo[*d*]oxazol-2-yl)-*N*-phenylbenzamide (4a)

M.P. 217-218 °C. IR (KBr) : 3050-3430 (br, m, -NH-), 1713 cm^{-1} (s, s, -CO-). ^{1}H NMR δ = 6.8-7.9 (m, 13H, Ar-H), 9.8 (s, 1H, -CO-NH, D$_2$O exchangeable); ^{13}C NMR δ = 116, 118, 119, 123, 123, 127, 128, 128, 130, 130, 131, 131, 134, 134, 153, 167; HRMS calcd. for C$_{20}$H$_{14}$N$_2$O$_2$ [M+H]$^+$ 314.8469. Found 314.8426.

2-(1*H*-Benzo[*d*]oxazol-2-yl)-*N*-(4-chlorophenyl)benzamide (4b)

M.P. 202-204 °C. IR (KBr): 3042-3457 (br, m, -NH-), 1711 cm^{-1} (s, s, -CO-). ^{1}H NMR δ = 6.8-7.9 (m, 12H, Ar-H),

9.9 (s, 1H, -CO-NH, D$_2$O exchangeable); ^{13}C NMR δ =116, 118, 119, 123, 123, 127, 128, 129, 130, 130, 131, 131, 134, 135, 153, 167. HRMS calcd. for C$_{20}$H$_{13}$ClN$_2$O$_2$ [M+H]$^+$ 349.4876. Found: 349.4849.

2-(1*H*-Benzo[*d*]oxazole-2-yl)-*N*-(4-methylphenyl)benzamide (4c)

M.P. 221-223 ºC. IR (KBr): 3065-3458 (br, m, -NH-), 1716 cm^{-1} (s, s, -CO-). ^{1}H NMR δ = 2.0 (s, 3H, -CH3), 6.8-7.9 (m, 12H, Ar-H), 9.8 (s, 1H, -CO-NH, D2O exchangeable); ^{13}C NMR δ = 23, 115, 118, 119, 123, 123, 127, 128, 128, 130, 130, 131, 131, 134, 134, 152, 167; HRMS calcd. for C$_{21}$H$_{16}$N$_2$O$_2$ [M+H]$^+$ 329.5833. Found 329.5837.

2-(1*H*-Benzo[*d*]oxazole-2-yl)-*N*-(4-bromophenyl)benzamide (4d)

M.P. 209-211 ºC. IR (KBr): 3048-3458 (br, m, -NH-), 1706 cm-1 (s, s, -CO-). ^{1}H NMR δ = 2.2 (s, 3H, -CH3), 6.8-7.9 (m, 12H, Ar-H), 9.8 (s, 1H, -CO-NH, D2O exchangeable); ^{13}C NMR δ = 116, 118, 119, 123, 123, 127, 128, 129, 130, 130, 131, 131, 134, 135, 153, 168. HRMS calcd. for C$_{20}$H$_{13}$BrN$_2$O$_2$ [M+H]$^+$ 393.3772. Found 393.3736.

2-(1*H*-Benzo[*d*]oxazole-2-yl)-*N*-(4-iodophenyl)benzamide (4e)

M.P. 211-213 ºC. IR (KBr): 3033-3425 (br, m, -NH-), 1713 cm^{-1} (s, s, -CO-). ^{1}H NMR δ = 6.8-7.9 (m, 12H, Ar-H), 9.8 (s, 1H, -CO-NH, D$_2$O exchangeable); ^{13}C NMR δ = 115, 119, 119, 122, 123, 127, 128, 128, 130, 130, 131, 132, 134, 134, 153, 167. HRMS calcd. for C$_{20}$H$_{13}$IN$_2$O$_2$ [M+H]$^+$ 441.1752. Found 441.1725.

2-(1*H*-Benzo[*d*]oxazole-2-yl)-*N*-(4-methoxyphenyl)benzamide (4f)

M.P. 139-141 ºC. IR (KBr): 3051-3462 (br, m, -NH-), 1712 cm^{-1} (s, s, -CO-). ^{1}H NMR δ = 3.6 (s, 3H, -OCH3), 6.8-8.0 (m, 12H, Ar-H), 9.8 (s, 1H, -CO-NH, D$_2$O exchangeable); ^{13}C NMR δ = 55, 116, 118, 119, 123, 123, 126, 128, 129, 131, 132, 132, 133, 134, 135, 153, 168. HRMS calcd. for C$_{21}$H$_{16}$N$_2$O$_3$ [M+H]$^+$ 345.2773. Found 345.2726.

2-(1*H*-Benzo[*d*]oxazole-2-yl)-*N*-(4-hydroxyphenyl)benzamide (4g)

M.P. >220 ºC. IR (KBr): 3058-3472 (br, m, -NH-), 1709 cm^{-1} (s, s, -CO-). ^{1}H NMR δ = 6.8-8.0 (m, 12H, Ar-H), 8.2 (s, 1H, -OH), 9.8 (s, 1H, -CO-NH, D$_2$O exchangeable); ^{13}C NMR δ = 114, 115, 117, 121, 123, 126, 127, 128, 131, 132, 132, 133, 134, 134, 150, 164. HRMS calcd. for C$_{20}$H$_{14}$N$_2$O$_3$ [M+H]$^+$ 331.1664. Found 331.1627.

2-(1*H*-Benzo[*d*]oxazole-2-yl)-*N*-(4-nitrophenyl)benzamide (4h)

M.P. 178-181 ºC; IR (KBr): 3052-3461 (br, m, -NH-), 1705 cm^{-1} (s, s, -CO-). ^{1}H NMR δ = 6.8-8.0 (m, 12H, Ar-H), 9.8 (s, 1H, -CO-NH, D$_2$O exchangeable); ^{13}C NMR δ = 115,

119, 119, 122, 123, 125, 127, 128, 130, 130, 131, 132, 134, 134, 153, 164. HRMS calcd. for C$_{20}$H$_{13}$N$_3$O$_4$ [M+H]$^+$ 360.4682. Found 360.4655.

RESULTS AND DISCUSSION

At the outset of this study, we heated a mixture of **1**, aniline (**2a**) and **3** at 100 ºC in water for 60 min resulting in the formation of (**4a**) (Table 1, entry 1) as illustrated in scheme 1.

R = (a) H, (b) Cl, (c) Me, (d) Br,
(e) I, (f) OMe, (g) OH, (h) NO$_2$
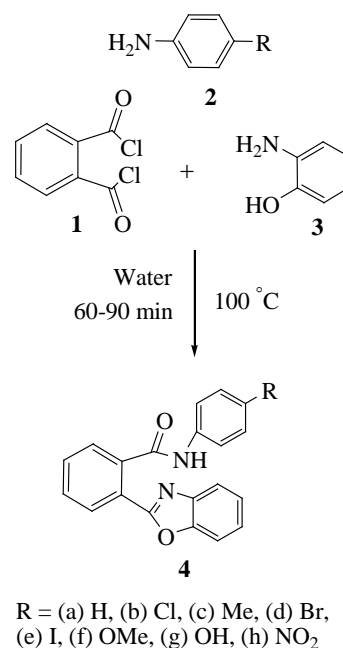
Scheme 1. Synthesis of **4a-h** in water.

The structure of the product was assigned on the basis of its spectral properties IR, NMR and MS. Then, this one-pot reaction of **1** (1 equiv.), **2a** (1 equiv.) and **3** (1 equiv.) was optimized by doing a series of experiments. Initially, the reaction was carried out in various solvents such as water, glycerol, PEG-600, ethylene glycol, DMF, DMSO and PPA and out of this, water at 100 ºC afforded the desired product with the best yield (Table 1, entry 1)**.** In the next step, we tested the effect of temperature at 25-30, 50-55 and 100 ºC in water as solvent. At 100 ºC, in water as solvent the desired product was given in 86 % yield.

With our optimized reaction conditions in hand (Table 1, entry 1), scope and limitations of the proposed method were investigated as shown in Table 2. First, we examined the substrate scope of anilines. The synthesis of **4a-4h** was carried out by heating the mixtures of **1, 2a-2h** and **3** in water at 100 ºC for 60-90 min. Products were obtained in good yield and no side products were detected. Their structures have been established on the basis of spectral properties such as IR, NMR and MS. (Scheme 1) (Table 2).

Two probable mechanisms (Schemes 2and 3) have been proposed to account for the formation of **4** in the one-pot synthesis from **1**, **2** and **3**. In the first mechanism**,** phthaldichloride **1** reacts with aniline **2** to form the imide intermediate **5** by liberating HCl. Then **5** was attacked by
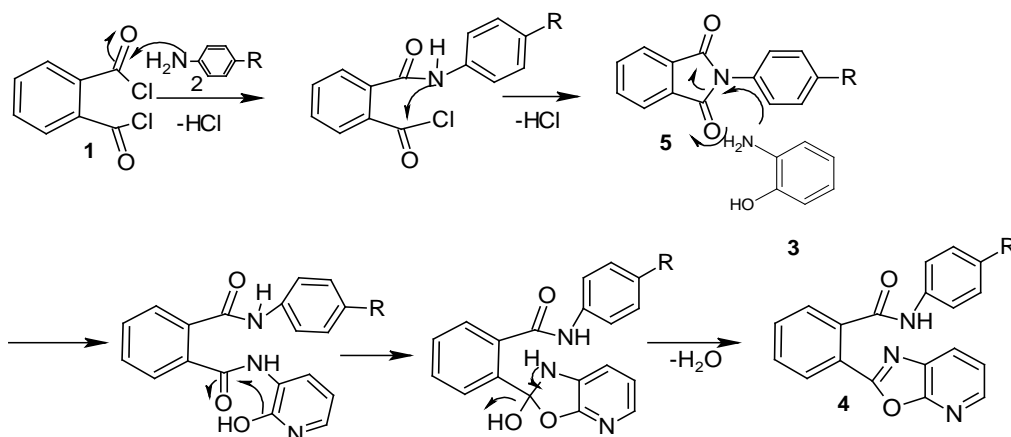
Scheme 2. First of the two proposed mechanisms of the synthesis.
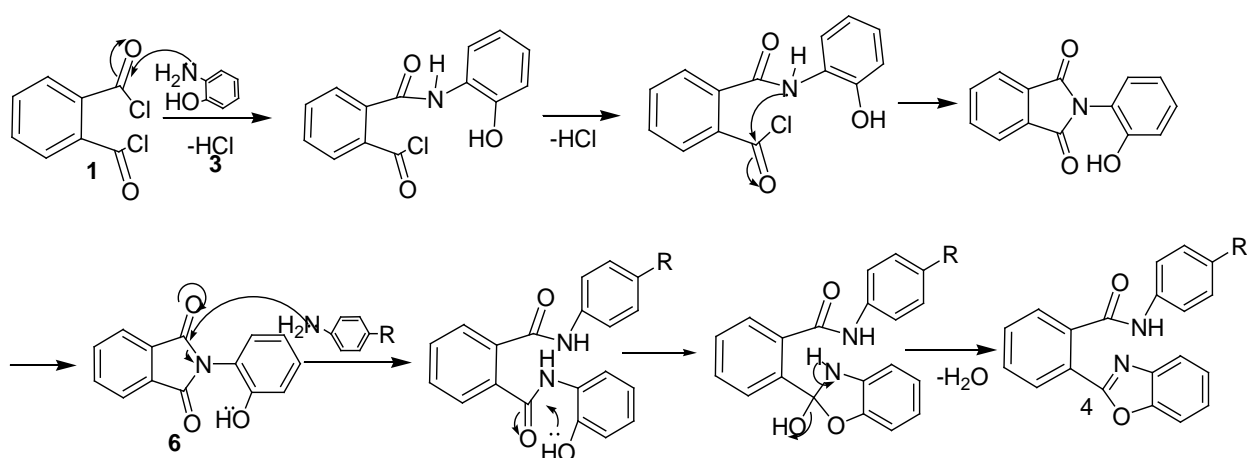
Scheme 3. Second of the two proposed mechanisms of the synthesis.

o-aminophenol **3** to form **4** in about two steps in the presence of HCl as catalyst.

Table 1. Effect of solvent and temperature on one-pot reaction of **1**, **2** and **3** to yield **4a**.

Entry	Solvent	Temp./º C	Time, min	Yield (% molar)
1	Water	100	60	86
2	Glycerol	100	120	80
3	PEG-600	100	120	78
4	Ethyleneglycol	100	100	75
5	DMF	100	90	60
6	DMSO	100	90	65
7	PPA	100	90	50
8	Water	25-30	600	80
9	Water	50-55	360	82

In the second probable mechanism, shown in scheme 3, a reaction of phthaldichloride **1** with *o*-aminophenol **3** yields the intermediate **6** by liberation of HCl.

Then, **6** was attacked by **2** to form **4** in two steps in the presence of HCl as catalyst. It seems likely that both the mechanisms are operating in this reaction. The difference between the two mechanisms in that the first mechanism involves a prior condensation of **1** with **2** followed by condensation with **3** whereas the second mechanism involves an initial condensation of **1** with **3** followed by condensation with **2**.

Table 2. Characterization data, reaction time and yields of **4a-4h** obtained from **1** , **2a-2h** and **3**.

Entry	Starting Material	Product obtained	Time, min	Yield≠
1	**2a**	**4a**	60	86
2	**2b**	**4b**	70	84
3	**2c**	**4c**	90	85
4	**2d**	**4d**	75	83
5	**2e**	**4e**	80	80
6	**2f**	**4f**	90	80
7	**2g**	**4g**	80	81
8	**2h**	**4h**	90	84

≠ Refers to yields of crude products only.

CONCLUSION

In summary, one-pot reaction has been developed for the synthesis of 2-(1*H*-benzo[*d*]oxazole-2-yl)-N-arylbenzamides with good yields. This method has an environmentally friendly procedure, easy operation and mild reaction conditions. It shows tolerance of a wide variety of functionalities as well as high reaction efficiency.

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