# Synthesis and antibacterial activity of some new imidazole, Imidazo[2,1-c]triazole and Imidazo[1,2-e]tetrazole derivatives

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### ABSTRACT

Reaction of 1-(3-phenylallylidene)thiosemicarbazide 2a-c with ethyl chloroacetate gave (3-phenylallylideneamino)-2-thioxoimidazolidin-4-one 3. Treatment of 3 with methyliodide, chloroacetic acid and with acetic anhydride gave the corresponding (3-phenylallylideneamino)imidazolidin-4-one derivatives 4, 5 and 6, respectively. Condensation of 3 with aromatic aldehydes yielded 5-arylidene-2-thioxoimidazolidin-4-ones 7 which react with acetic anhydride and with hydrazine to give the 1-acetyl-2-thioxoimidazolidin-4-one 8 and 2-hydrazinoimidazolidin-4-one 9, respectively. Reaction of 9 with acetic anhydride, carbon disulfide and with cyclohexanone gave the corresponding imidazo[2,1-c]triazoles 10, 11, and 13, respectively. The antibacterial activity of the synthesized compounds was also studied.

Key words: Imidazoles, Imidazo[1,2-e]tetrazole, Imidazo[2,1-c][1,2,4]triazole, antibacterial activity.

### INTROCDUCTION

Imidazol-thione derivatives are playing an important role in organic synthesis and are showing wide range of applications as therapeutics<sup>1-3</sup> as well as fungicides and herbicides<sup>4</sup>. Among these derivatives the S-glucosylated imidazolones<sup>5</sup> exhibit high activity against the herpes simple virus<sup>6</sup> (HSV), the human-immune deficiency virus<sup>7</sup> (HIV). The 1-aminoimidazolone is an antimicrobial drug for the treatment of urinary tract infections,8,9 muscle relaxant and as drug for cardiac arrhythmia. Phenylimidazolone and 5,5diphenylimidazolidin-2,4-dione were used as anticonvulsants.<sup>10</sup> Imidazolone-thione derivatives were reported as inhibitors of serine protease<sup>11</sup> and liver glycogen phosphorylases.<sup>12</sup> We here report a simple route to some new imidazole, imidazo[2,1-c]triazole and imidazo[1,2-e]tetrazole derivatives of potential biological activity.

### **RESULTS AND DISCUSSION**

Synthesis of 1-(3-phenylallylidene) thiosemicarbazide 2 was performed via the condensation of cinnamaldehyde 1 with thiosemicarbazide in ethanol under reflux according to literature procedure.13 Treatment of the thiosemicarbazone 2 with ethyl chloroacetate in ethanol, in the presence of sodium acetate, at reflux temperature yielded 3-(3-phenylallylideneamino)-2thioxoimidazolidin-4-one 3. The structure of the latter product was confirmed from its elemental and spectral analyses. Its IR spectrum showed absorption bands at 3261 and 1706 due to NH and C=O functions, respectively. Its <sup>1</sup>H NMR spectrum revealed three singlet signals at d 3.40, 8.50 and 11.30 corresponding to NCH<sub>2</sub>CO, CH = N and NH protons, respectively, in addition to an aromatic multiplet at d 6.81-7.81 due to aromatic and olefinic protons. Also, the mass spectrum of 3 showed a peak at m/z 245 due to its molecular ion.

Reaction of 3-(3-phenylallylideneamino)-2thioxoimidazolidin-4-one 3 with methyl iodide in the presence of anhydrous potassium carbonate in ethanol led to the formation of the 2methylthioimidazolidin-4-one derivative 4 as outlined in Scheme 1. The structure of compound 4 was confirmed from its analytical and spectroscopic data.

Similarly, compound 3 underwent smooth *N*-alkylation when treated with chloroacetic acid in refluxing ethanol, in the presence of trimethyl amine, to afford 2-thioxoimidazolidine-1-acetic acid derivative 5 based on the elemental and spectral analyses.

Reaction of 3-(3-phenylallylideneamino)-2thioxoimidazolidin-4-one 3 with acetic anhydride under reflux resulted in the formation of the corresponding 1-acetyl derivative 6. The structure of compound 6 was elucidated on the basis of the analytical and spectroscopic (IR, <sup>1</sup>H and <sup>13</sup>C NMR and MS) data as well as chemical transformations that outlined in Scheme 1. Compound 6 revealed two SP<sup>3</sup> carbons at d 20.99 and 72.70 in addition to nine SP<sup>2</sup> carbons. Its <sup>1</sup>H NMR exhibited three singlet signals at d 2.31 and 3.51 corresponding to COCH<sub>2</sub>, NCH,CO and CH=N protons, respectively besides the aromatic multiplet in the region d 6.81-7.81. The IR spectrum was free of any NH absorption bands and showed two C=O absorption bands at 1730 and 1715 cm<sup>-1</sup>. In addition, its mass spectrum showed a molecular ion peak at m/z 287.

Fusion of compound 3 with aromatic aldehydes (4-chlorobenzaldehyde and furfural) in the presence of few drops of piperidine without solvent led to the formation of the corresponding 5arylidine derivatives 7a,b. Treatment of compound 7a with acetic anhydride at reflux temperature afforded the corresponding 1-acetyl-5-arylidene imidazolidine derivative 8. The structure of compound 8 was established on the basis of its analytical and spectroscopic data as well as the alternative synthesis that outlined in Scheme 1. Thus, compound 8 was alternatively obtained via the condensation of compound 6 with 4chlorobenzaldehyde in refluxing acetic acid in the presence of anhydrous sodium acetate. The product was in complete agreement with that obtained above from 7a.

Next, heating 4 with hydrazine hydrate in ethanol under reflux condition resulted in the formation of 2-hydrazinyl-1H-imidazol-5-one derivative 9 as shown in scheme 1. The structure of 9 was confirmed from the analytical and spectroscopic analyses of the isolated reaction product.

When compound 9 was heated in acetic anhydride under reflux it gave a single product that was identified as 7-(3-phenylallylideneamino)-3methyl-5H-imidazo[2,1-c][1,2,4]triazol-6-one 10 as shown in scheme 2.

Treatment of 2-hydrazinyl-1H-imidazol-5one derivative 9 with carbon disulphide in pyridine under reflux heating resulted in the formation of a single product that was identified as 7-(3phenylallylideneamino)-2,3-dihydro-3-thioxo-5Himidazo[2,1-c][1,2,4]-triazol-6-one 11 as shown in scheme 2. Nitrosation of 2-hydrazinyl-1H-imidazol-5-one derivative 9 with sodium nitrite and hydrochloric acid proceeded smoothly at 50 °C to give the imidazo[1,2-e]tetrazol-5-one derivative 12 as depicted in scheme 2.

Condensation of compound 9 with cyclohexanone in refluxing acetic acid furnished a single product named as 7-[(3-phenylally lideneamino]-3-spirocyclohexyl-2,5,6,7-tetrahydro-3H-imidazo[2,1-c]-1,2,4-triazol-6-one 13 as outlined in scheme 2. Structures of the products 10-13 were confirmed from the elemental and spectral analyses of the reaction products.

#### **EXPERIMENTAL**

Melting points were measured on a MEL-TEMP II apparatus. Infrared spectra were measured in KBr with Perkin–Elmer FT IR 5300 Spectrometer. The <sup>1</sup>H-NMR spectra were performed on a Varian Mercury 300 MHz Spectrometer in DMSO-d<sub>6</sub> using TMS as an internal standard. Mass spectra were obtained in a Jeol JMS D-300 Spectrometer operating at 70 eV. The elemental analyses were conducted by the Microanalytical Center, Cairo University. 1-(3-Phenylallylidene)thiosemicarbazide<sup>13</sup> 2 was prepared following the literature procedure

### Synthesis of 3-(3-phenylallylideneamino)-2thioxoimidazolidin-4-one 3

A mixture of 2 (10 mmol) and ethyl chloroacetate (I0 mmol) in ethanol (50 ml) in presence of anhydrous sodium acetate (30 mmol) was heated under reflux for 4 hr. After cooling to room temperature, the reaction mixture was poured into water. The resulting solid was filtered off, washed with hot water, dried and recrystallized from methanol to give 3 as yellow crystals in 68% yield. m.p. 211 °C; IR (KBr) n 3261 (NH), 1706 (C=O), 1632 (C=C), 1396 (C=S) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>c</sub>) d 3.40 (s, 2H, NCH, CO), 6.81-7.81 (m, 7H, ArH and olefinic-H), 8.50 (d, 1H, CH=N), 11.30 (br. s, 1H, NH); MS m/z (%) 245 (M<sup>+</sup>, 81.30), 218 (25.30), 185 (11.50), 170 (35.30), 142 (27.20), 129 (65.30), 119 (25.20), 115 (85.50), 103 (25.60), 91 (30.30), 77 (18.50), 51 (25). Anal. Calcd for C<sub>10</sub>H<sub>11</sub>N<sub>2</sub>OS: C, 58.78; H, 4.49; N, 17.14; S, 13.06. Found: C, 58.58; H, 4.31; N, 17.00, S, 12.87.

### Synthesis of 1-(3-phenylallylideneamino)-2-(methylthio)-1H-imidazol-5(4H)-one 4

A mixture of 3 (I0 mmol), methyl iodide (10 mmol) and anhydrous potassium carbonate (30 mmol) in ethanol (50 ml) was heated under reflux for 4hrs. The reaction mixture was then cooled and poured onto water. The solid formed was filtered off, washed with water, dried and recrystallized from ethanol to give 4 as pale yellow crystals in 61% yield. m.p. 147 °C; IR (KBr) n 1710 (C=O), 1625 (C=N), 1600, 1597 (C=C) cm<sup>-1</sup>; MS m/z (%) 260 (M<sup>+</sup>+1, 15.30), 259 (M<sup>+</sup>, 39.50), 184 (13.50), 129 (100), 115 (98), 102 (35.30), 84 (16.20), 77 (23.30), 63 (13.50), 51 (35.50). Anal. Calcd for C<sub>13</sub>H<sub>3</sub>N<sub>3</sub>OS: C, 60.23; H, 5.02; N, 16.22; S, 12.36. Found: C, 60.03; H, 4.89; N, 16.01; S, 12.13.

### Synthesis of (3-(3-phenylallylideneamino)-4oxo-2-thioxoimidazolidin-1-yl)acetic acid 5

A mixture of 3 (10 mmol) and chloroacetic acid (10 mmol) in ethanol (30 ml) in presence of trimethyl amine (1 ml) was heated under reflux for 4hrs. The reaction mixture was cooled and poured onto 5% hydrochloric acid in ice. The crude product was filtered off, washed with water, dried and purified by recrystallization from methanol to give 5 as yellow crystals in 63% yield. M.p 235 °C, IR (KBr) n 3350–2850 (br. OH), 1713, 1701 (2 C=O), 1629 (C=N), 1601, 1583 (C=C), 1384 (C=S) cm<sup>-1</sup>; MS m/ *z* (%): 303 (M<sup>+</sup>, 30.30), 256 (15.50), 231 (15.40), 203 (15.30), 187 (51.30), 145 (13.50), 130 (25.00), 115(73.50), 102 (20.30), 77 (30.30), 61(100). Anal. Calcd. for  $C_{14}H_{13}N_3O_3S$ : C, 55.43; H, 4.32; N, 13.85; S, 10.57. Found: C, 55.27; H, 4.08; N, 13.55; S, 10.33.

# Synthesis of 1-acetyl-3-(3-phenylally lideneamino)-2-thioxoimidazolidin-4-one 6

A solution of 3 (10 mmol) in acetic anhydride (25 ml) was heated under reflux for 2hr, then cooled and poured onto ice-water. The resulting product was filtered off, washed with water, dried and recrystallized from benzene to give 6 as yellow crystals in 56% yield. m.p. 112 °C, IR (KBr) n 1730, 1715 (2 C=O), 1635 (C=N), 1601, 1595 (C=C), 1381 (C=S) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>c</sub>) d 2.31 (s, 3H, COCH<sub>2</sub>), 3.51 (s, 2H, NCH<sub>2</sub>CO), 6.81-7.81 (m, 7H, Ar-H and H-olefinic), 8.23 (d, 1H, CH=N); <sup>13</sup>C NMR (DMSO-d<sub>c</sub>) d 179.2, 164.4, 163.3, 143.3, 134.9, 128.5, 128.4, 126.8, 121.3, 72.7, 20.9; MS m/z (%): 287 (M<sup>+</sup>, 49.50), 245 (80.30), 218 (23.30), 190 (3.50), 168 (25.30), 142 (26.50), 129 (81.20), 116 (39.20), 115 (100%), 103 (16.20), 91 (10.20), 77 (25.50), 63 (38.50), 51 (32.30). Anal. Calcd. for C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>S: C, 58.54; H, 4.53; N, 14.63; S, 11.15. Found: C, 58.26; H, 4.31; N, 14.44; S, 10.93.

### Synthesis of 5-arylidene-3-substituted-2thiohydantoins 7a,b

A mixture of 3 (10 mmol), and the appropriate aromatic aldehydes (4chlorobenzaldehyde or 2-furfural) (10 mmol) and piperidine (1 ml) was heated at 120-125 °C for 1hr without solvent. The reaction mixture was then left to cool to room temperature and acidified with dilute hydrochloric acid (2%). The crude product was filtered off, washed with water, dried and purified by recrystallization from the suitable solvent to give compounds 7a,b.

# 5-(4-Chlorobenzylidene)-3-(3-phenylallylid eneamino)-2-thioxoimidazolidin-4-one 7a

Yellow crystals (AcOH), yield 83%, m.p. 255 °C, IR (KBr) n 3223 (NH), 1708 (C=O), 1640 (C=N), 1586, 1562 (C=C), 1381 (C=S) cm<sup>-1</sup>; MS m/ z (%) 369 (M<sup>+</sup>+2, 15.30), 367 (M<sup>+</sup>, 46.30), 333 (16.70), 194 (13.30), 187 (9.50), 160 (100), 155 (35.50), 128 (73.30), 124 (26.30), 101 (27.20), 89 (49.80), 77 (24.20), 51 (25.50). Anal. Calcd .for



Scheme 1.



Scheme 2.

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C<sub>19</sub>H<sub>14</sub>N<sub>3</sub>CIOS: C, 62.13; H, 3.81; N, 11.44; S, 8.72 .Found: C, 62.01; H, 4.01; N, 11.47; S, 8.66.

### 5-(2-Furylidene)-3-(3-phenylallylideneamino)-2thioxoimidazolidin-4-one 7b

Yellow crystals (MeOH), yield 61%, m.p. 247 °C , IR (KBr) n 3219 (NH), 1703 (C=O), 1629 (C=N), 1603, 1583 (C=C), 1391 (C=S) cm<sup>-1</sup>; MS m/ z (%) 324 (M<sup>+</sup>+1, 13.0), 323 (M<sup>+</sup>, 73.20), 305 (25.50), 256 (15.20), 244 (60.30), 231 (20.30), 218 (30.20), 168 (25.30), 145 (17.20), 130 (56.30), 115 (100), 103 (20.30), 89 (17.20), 77 (31.20), 61 (92.30). Anal Calcd for  $C_{17}H_{13}N_3O_2S$ : C, 63.16, H, 4.02; N, 13.00, S, 9.91. Found: C, 63.01, H, 3.98, N, 12.79, S, 9.69.

# 1-Acetyl-5-(4-chlorobenzylidene)-3-(3phenylallylideneamino)-2-thioxoimidazolidin-4one 8

A solution of the imidazolidinethione derivative 7a (10 mmol) in acetic anhydride (25 ml) was heated under reflux for 2h, then left to cool to room temperature and poured onto ice-water. The solid obtained was filtered off, washed with water, dried and recrystallized from benzene to give 8 as pale yellow crystals in 51% yield. m.p. 125 °C; IR (KBr) n 1715, 1705 (2 C=O), 1635 (C=N), 1589, 1575 (C=C), 1384 (C=S) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>e</sub>) d 2.53 (s, 3H, COCH2), 6.90-7.81 (m, 13H, Ar-H and olefinic-H); MS m/z (%) 411 (M+2, 21.30) 409 (M<sup>+</sup>, 53.20), 375 (56.50), 367 (56.50), 314 (49.50), 256 (17.20), 229 (16.20), 194 (16.50), 186 (21.30), 160 (100), 155 (76.30), 129 (36.20), 89 (30.20), 77 (24.20), 63 (23.10), 51 (23.20). Anal. Calcd. for C<sub>21</sub>H<sub>46</sub>N<sub>2</sub>ClO<sub>2</sub>S: C, 61.61; H, 3.91; N, 10.27; S, 7.82. Found: C, 61.44; H, 3.76; N, 10.08; S, 7.66.

To a mixture of compound 6 (2 mmol) and 4-chlorobenzaldehyde (2 mmol) in acetic acid (10 mL), anhydrous sodium acetate 0.3 g were added and the mixture was refluxed for 3 hr, then cooled. After crystallization from benzene the product was obtained in 59% yield and was in complete agreement with that obtained above from 7a.

# Synthesis of 1-(3-phenylallylideneamino)-2hydrazinyl-1H-imidazol-5(4H)-one 9

A mixture of 4 (10 mmol) and hydrazine hydrate (12 mmol) in ethanol (30 ml) was heated under reflux for 4 h, then left to cool to room temperature. The resulting solid was filtered off washed with dilute ethanol, dried and purified by recrystallization from ethanol to give compound 9 as pale yellow crystals in 58% yield. M.p. 159 °C, IR (KBr) n 3410, 3175 (NH<sub>2</sub>), 3225 (NH), 1703 (C=O), 1630 (C=N), 1602, 1583 (C=C) cm<sup>-1</sup>; MS *m/z* (%) 244 (M<sup>+</sup>+1, 25.10), 243 (M<sup>+</sup>, 22.50), 129 (100), 116 (30.20), 115 (100), 102 (33.50), 89 (13.20), 77 (25.30), 63 (13.20), 51 (30.20). Anal. Calcd. for  $C_{12}H_{13}N_5$ O: C, 59.26; H, 5.35; N, 28.81. Found: C, 59.02; H, 5.15; N, 28.69.

# 7-(3-Phenylallylideneamino)-3-methyl-5Himidazo[2,1-c][1,2,4]triazol-6-one 10

A solution of 9 (10 mmol) in acetic anhydride (25 ml) was heated under reflux for 4 hr, then cooled and poured into ice-water (20 mL) .The solid formed was filtered off, washed with water, dried and purified by recrystallization from ethanol to give 10 as yellow crystals in 56% yield. m.p 248 °C, IR (KBr): 1710 (C=O), 1632 (C=N), 1603, 1581 (C=C) cm<sup>-1</sup>; MS (*m*/*z*) %: 267 (M<sup>+</sup>, 76.50), 130 (25.30), 115 (100), 103 (16.50), 89 (13.30), 77 (25.50), 63 (11.50), 51 (18.20). Anal. Calcd. for  $C_{14}H_{13}N_5O$ : C, 62.92, H, 4.87, N, 26.22. Found: C, 62.73, H, 4.68, N, 26.08.

### 7-(3-Phenylallylideneamino)-2,3-dihydro-3thioxo-5H-imidazo[2,1-c][1,2,4]triazol-6-one 11

A mixture of 9 (10 mmol) and carbon disulphide (30 mmol) in pyridine (25 mL) was heated under reflux for 4 hr. After the reaction was complete, the reaction mixture was left to cool to room temperature and then poured on to cold aqueous hydrochloric acid (2%). The resulting product was filtered off, washed with water, dried and purified by recrystallization from ethanol to give 11 as yellow crystals in 63% yield. m.p 216 °C, IR (KBr): 3215 (NH), 1712 (C=O), 1631 (C=N), 1601, 1583 (C=C), 1389(C=S) cm<sup>-1</sup>; MS (*m*/*z*) %: 283 (M<sup>+</sup>, 100), 147 (36.20), 133 (89.20), 118 (50.30), 103 (10.20), 89 (18.20), 77 (25.30), 63 (11.20). Anal.Calcd. for C<sub>13</sub>H<sub>11</sub>N<sub>5</sub>OS: C, 54.74, H, 3.86, N, 24.36, S, 11.23.Found: C, 54.54, H, 3.68, N, 24.33, S, 11.03.

### 4-(3-Phenylallylideneamino)-4H-imidazo[1,2e]tetrazol-5-one 12

A mixture of 9 (10 mmol), sodium nitrite (30 mmol) and hydrochloric acid (10 mL) in acetic acid (10 mL) was heated 50 °C for 3 hr .The reaction mixture was then left to cool to room temperature

Compd. No.	Eshrsia	Staphylococcus	Proteus	E. coli	Salomonella
2a	+++ve	+ve	++ve	++ve	+++ve
2b	+++ve	+++ve	+++ve	+++ve	+ve
2c	+ve	+ve	+ve	++ve	+ve
3a	+ve	+ve	+ve	++ve	+ve
3b	+ve	+ve	+ve	+ve	+++ve
4a	+ve	++ve	-ve	++ve	+++ve
5a	+ve	+++ve	+++ve	+++ve	+++ve
6a	+++ve	+++ve	-ve	+++ve	+++ve
7a	+ ve	+ ve	+ ve	+ ve	++ve
7b	+ ve	+ ve	++ ve	++ ve	++ ve
8	+ ve	+++ ve	+++ ve	++ ve	+ ve
9a	+++ve	+++ve	+ve	+++ve	+++ve
9b	+++ve	+++ve	+++ve	+++ve	+ve
10	+ve	+ve	+ve	++ve	+ve
11	+ve	+ve	+ve	++ve	+ve
12	+ve	-ve	-ve	-ve	-ve
13	+ve	++ve	-ve	++ve	+++ve

 Table 1: Antibacterial activity of the synthesized compounds

- No antibacterial activity ,+ Mild activity ,++ Moderate activity ,+++ Marked activity

and poured into water (20 mL). The crude product was filtered off, washed with water, dried and purified by recrystallization from chloroform to give 12 as pale yellow crystals in 61% yield. m.p. 117 °C; IR (KBr): 1708 (C=O), 1632 (C=N), 1603, 1581 (C=C) cm<sup>-1</sup>; MS (*m/z*) %: 254 (M<sup>+</sup>, 51.30), 188 (6.30), 160(100), 144 (89.90), 129 (41.50) 115 (53.30), 104 (11.20), 91 (15.20), 77 (13.50), 63 (16.70), 51 (18.20). Anal. Calcd. For  $C_{12}H_{10}N_6O$ : C, 56.70, H, 3.94, N, 33.07. Found: C, 56.48, H, 3.77, N, 32.98.

## 7-[(3-Phenylallylideneamino]-3-spirocyclohexyl-2,5,6,7-tetrahydro-3H-imidazo[2,1-c]-1,2,4triazol-6-one 13

A mixture of 9 (10 mmol) and cyclohexanone (10 mmol) in acetic acid (30 mL) was heated under reflux for 3hr, then cooled and poured onto water (20 mL). The solid obtained was filtered off, washed with water, dried and purified by recystallization from toluene to give 13 as yellow crystals in 67% yield. m.p. 162 °C; IR (KBr): 3215 (NH), 1703 (C=O), 1629 (C=N), 1603, 1590 (C=C) cm<sup>-1</sup>; MS (*m/z*) %: 323 (M<sup>+</sup>, 50.30), 148 (26.30), 133 (51.20), 129 (100), 118 (33.20), 102 (31.20), 78 (18.20), 63 (16.20), 51 (25.30). Anal. Calcd. for  $C_{18}H_{21}N_5O$ : C, 66.87; H, 6.50; N, 21.67. Found: C, 66.66; H, 6.28; N, 21.43.

### **Biological activity**

Applying the agar plate diffusion<sup>14,15</sup> all the newly synthesized compounds were screened *in vitro* for antibacterial activity against *Eshrsia*, *Staphylococcus*, *Proteus*, *Escherichia coli* and *Salomonella*. The compounds were tested at 100 mg/ml concentration (DMSO) and the activity was determined by measuring the zone of inhibition. The screening results given in Table 1 indicated that most of the synthesized compounds exhibited high antibacterial activities against all types of the above mentioned bacteria.

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