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Research Article

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Efficient synthesis, characterization and biological evaluation of some new atophan carbohydrazide derivatives

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ABSTRACT

*A series of newly Atophans (Cinchophen, 2-phenylcinchoninic acid) heterocycles have been synthesized by employing 2-phenylquinoline-4-carboxylic acid (cinchophen) as starting material with the aim of evaluating their antimicrobial activity. The key intermediate 2-phenylquinoline-4-carbohydrazide (**3**) was smoothly synthesized by reaction of phenylcinchoninic ethyl ester with hydrazine hydrate in ethanol. The structures of synthesized compounds were confirmed on the basis of their elemental analysis and spectral results (IR, ^{1}H and ^{13}C NMR). The synthesized compounds were screened for their bactericidal and fungicidal activities. The preliminary results revealed that some of the compounds exhibited promising antimicrobial activities.*

Keywords: Atophan, 2-phenylquinoline-4-carbohydrazide, aromatic Schiff's bases, azido(2-phenylquinolin-4-yl)methanone, biological activity

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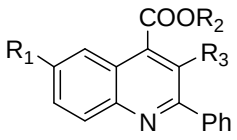
INTRODUCTION

Chemistry of quinoline and its derivatives continues to attract interest due to their importance as synthetic intermediates[1-3] well recognized by synthetic and biological chemists and as the key structural element found in a large array of natural products[4-5] and pharmaceuticals[6-8].

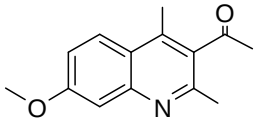
Studies have discovered that these compounds exhibit diverse medical functions such as anti-inflammatory[9], antiallergic[10], antimalarial[11], antibacterial[12], antiproliferative[13], anticancer[14], antiparasitic[15], antidepressive[16], antidiabetic[17], analgesic[18], antipsychotic[19], cardiovascular[20], antileishmanial[21], antiplatelet[22], antiviral[23], fungicide[24] and pesticide agents[25].

Among the various quinoline compounds, cinchophenic acid derivatives are the heterocyclic compounds with considerable therapeutic and pharmacological properties. 2-Phenylquinoline-4-carboxylic (Atophan, Quinophan and Phenaquin are some other names for the same drug).

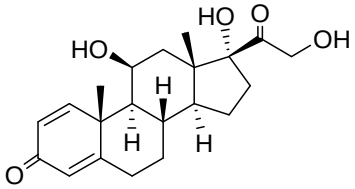
Weintraud[26] in 1911 introduced the agent as a medicine in the United States under the proprietary name "Atophan" for the treatment of rheumatism (Fig. 1) and gout (acequinoline, cinchophen, neocinchophen and oxycinchophen)[27].



a: Cinchophen; $R^1 = R^2 = R^3 = H$
b: Neocinchophen; $R^1 = R^2 = Me$, $R^3 = H$
c: Oxycinchophen; $R^1 = R^2 = H$, $R^3 = OH$



Acequinoline



Prednisolone

Figure 1. Quinoline skeleton containing pharmaceuticals

While the Chemical Foundation and the Council on Pharmacy and Chemistry adopted the coined nonproprietary name "Cinchophen" and a license has been issued only to the Abbott Laboratories. Cinchophen has been used as an antirheumatic agent for more than 60 years, however, the drug caused acute and degenerative hepatitis[28] in patients which limited its clinical use by the 1930s due to the discovery that cinchophen can cause serious liver damage. Even after more than a century of pharmacotherapy and research, to date, cinchophen shown to exert remarkable biological activity in many active pharmaceutical ingredients[29,30] and have been proved to be a powerful analgesic, antimicrobial and antifungal agents[31]. Moreover this drug is still used in combination with Prednisolone.

Owing to remarkable biological activities of cinchophen derivatives, there has been an extensive interest in the synthesis of its biological active derivatives, structural modification and pharmacological properties still continues unabated[32-34].

In our previous work, we incorporated cinchophen in the construction of substituted 4,5-dihydrocyclopenta[*de*]quinoline derivatives *via* Friedel-Crafts cyclialkylations of suitable synthesized alcohols[35]. In connection with our previous studies in the synthesis of diverse of biological significance heterocycles[36-44], herein, we wish to report the synthesis and antimicrobial evaluation of some novel atophan derivatives.

EXPERIMENTAL SECTION

All reagents were purchased from Merck, Sigma or Aldrich Chemical Co. and were used without further purification. Melting points were measured on a digital Gallenkamp capillary melting point apparatus and are uncorrected. The IR spectra were determined with a Pye Unicam SP3-100 spectrophotometer using the KBr wafer technique (ν cm^{-1}). The ^1H NMR and ^{13}C NMR spectra were recorded recorded on a Bruker ARX 400 MHz FT-NMR spectrometer (400 MHz for ^1H, 100 MHz for ^{13}C) at the Faculty of Science, University of King Saoud, Saudi Arabia, Riyadh using $CDCl_3$ and DMSO-d_6 solvents with TMS as internal standard. Chemical shifts (δ) and *J* values are reported in ppm and Hz, respectively. Elemental analyses were performed on a Perkin-Elmer 2400 Series II analyzer. The mass spectra were performed by JEOL JMS 600 spectrometer at an ionizing potential of 70 eV using the direct inlet system. Reactions were monitored by thin layer chromatography (TLC) using precoated silica plates visualized with UV light. Flash column chromatography was performed on silica gel and basic alumina.

*2-Phenylquinoline-4-carbohydrazide (**3**).*
Following the standard literature procedure[47], this compound was obtained in a series of two consecutive steps starting with 2-phenylquinoline-4-carboxylic acid. The spectral data of the pure crystallized product are given in the following: White crystals; 86%, m.p. 214-16 ºC (ethanol); Anal. Calcd. for $C_{16}H_{13}N_3O$ (263); C, 73.00; H, 4.94; N, 15.96. Found; C, 73.27; H, 4.85; N, 16.22 %; ^{13}C-NMR (100 MHz, $CDCl_3$, δ/ppm): 166.31, 158.72, 142.53, 148.45, 142.27, 138.78, 130.78, 130.47, 130.09, 129.50, 127.85, 127.67, 125.97, 124.17, 119.67, 117.51; MS (m/z, (relative abundance, %)): 263 (100), 247 (73), 232 (25), 204 (84), 186 (33), 170 (14), 155 (10), 127 (9), 90 (12), 75 (4), 51 (7).

*1-(2-Phenyl-quinoline-4-carbonyl)-pyrazolidine-3,5-dione (**4**).*
A mixture of 2-phenyl-quinoline-4-carboxylic acid hydrazide **3** (1.09 g, 4 mmol) and diethyl malonate (0.64 g, 4 mmol) in acetic acid (20 ml) was heated under reflux for overnight. The reaction mixture was then poured with stirring into ice-cold water and the obtained precipitate was collected by filtration, washed with water and dried. Crystallization from diluted ethanol gave (0.95 g, 72 %) of pure **4** as buff needles; m.p. 256-58 °C; Anal. Calcd. for $C_{19}H_{13}N_3O_3$ (331); C, 68.88; H, 3.92; N, 12.68. Found; C, 68.73; H, 3.97; N, 12.52 %; IR (KBr, cm^{-1}): 3260 (NH), 3091 (CH) (Aromatic), 2986 (CH) (pyrazole), 1647, 1632, 1614 (C=O) (amides), 1590, 1460, 1445 (C=C) (Aromatic), 1335 (C-N), 1180, 745; ^1H-NMR (400 MHz, DMSO-d_6, δ/ppm): 3.39 (2H, s, CH_2), 7.51-8.27 (9H, m,

Ar-H), 8.35 (1H, s, pyridine-H); 12.05 (1H, s, NH); ^{13}C-NMR (100 MHz, DMSO-d_6, δ/ppm): 170.34, 168.37, 165.36, 158.72, 146.83, 142.54, 139.71, 134.52, 132.26, 130.24, 129.02(2C), 127.12 (3C), 123.51, 121.34, 119.62, 46.91; MS (m/z, (relative abundance, %)): 331 (25), 305 (12), 263 (37), 248 (4), 231 (79), 204 (100), 176 (10), 149 (6), 95 (2), 93 (19), 76 (5), 74 (14), 51 (7).

*5-Methyl-1-(2-phenyl-quinoline-carbonyl)-1,2-dihydro-pyrazol-3-one (**5**).*

A mixture of 2-phenyl-quinoline-4-carboxylic acid hydrazide **3** (1.09 g, 4 mmol) and ethyl acetoacetate (0.52 g, 4 mmol) in acetic acid (20 ml) was heated under reflux for overnight. The reaction mixture was then poured into ice-cold water and the obtained precipitate was collected by filtration, washed with water, dried and crystallized from diluted ethanol to give **5** (0.68 g, 52 %) as pale yellow crystals; m.p. 332-34 °C; Anal. Calcd. for $C_{20}H_{15}N_3O_2$ (329); C, 72.94; H, 4.55; N, 12.76. Found; C, 72.88; H, 4.35; N, 12.93 %; IR (KBr, cm^{-1}): 3330 (NH), 3112 (CH) (Aromatic), 2981 (CH) (pyrazole), 1683, 1668 (2 CO), 1600, 1565, 1472, 1443 (C=C) (Aromatic), 1310 (C-N), 1030, 758; ^{1}H-NMR (400 MHz, DMSO-d_6, δ/ppm): 2.42 (3H, s, CH_3), 7.65-8.65 (11H, m, Ar-H; pyridine-H; pyrazole-H), 10.22 (1H, s, NH); ^{13}C-NMR (100 MHz, DMSO-d_6, δ/ppm): 165.23, 161.92, 158.71, 1464.83, 146.51, 142.54, 139.71, 134.52, 132.81, 130.27, 129.01 (2C), 127.11 (3C), 123.52, 121.31, 119.63, 97.66, 23.51; MS (m/z, (relative abundance, %)): 329 (42), 305 (0.5), 276 (1), 249 (8), 248 (14), 231 (39), 228 (11), 205 (29), 204 (100), 203 (11), 176 (2), 146 (14), 94 (3), 93 (7), 76 (2), 74 (3), 43 (6).

*(3,5-Dimethyl-pyrazol-1-yl)-(2-phenyl-quinolin-4yl)methanone (**6**).*

A mixture of 2-phenyl-quinoline-4-carboxylic acid hydrazide **3** (1.09 g, 4 mmol) and acetylacetone (0.4 g, 4 mmol) in acetic acid (20 ml) was heated under reflux for overnight. The reaction mixture was then poured into ice-cold water and the obtained precipitate was collected by filtration, washed with water, dried and crystallized from diluted ethanol to give **6** (0.72 g, 56 %) as white needles; m.p. 208-10 °C; Anal. Calcd. for $C_{21}H_{17}N_3O$ (327); C, 77.06; H, 5.19; N, 12.84. Found; C, 77.25; H, 5.04; N, 12.68 %; IR (KBr, cm^{-1}): 3092 (CH) (Aromatic), 2987(CH) (pyrazole), 1706 (C=O) (amide), 1594, 1577, 1445, 1435 (C=C) (Aromatic), 1382, 1020, 743; ^{1}H-NMR (400 MHz, DMSO-d_6, δ/ppm): 2.35 (6H, s, 2 CH_3), 7.65-8.85 (11H, m, Ar-H); ^{13}C-NMR (100 MHz, DMSO-d_6, δ/ppm): 186.26, 158.72, 149.12 (2C), 146.81, 142.53, 139.71, 134.52, 132.81, 132.24, 129.10 (2C), 127.12 (3C), 123.51, 121.32, 119.61, 105.66, 13.82, 7.11. MS (m/z, (relative abundance, %)): 327 (29), 276 (58), 248 (59), 231 (7), 219 (14), 205 (83), 204 (100), 203 (56), 202 (53), 175 (20), 165 (11), 151 (12), 124 (15), 104 (2), 94 (12), 93 (54), 74 (37), 51 (19), 45 (5).

*5-(2-Phenylquinolin-4-yl)-3H-[1,3,4]oxadiazole-2thione (**7**).*

A mixture of 2-phenyl-quinoline-4-carboxylic acid hydrazide **3** (1.09 g, 4 mmol) and carbon disulfide (5 ml) in pyridine (20 ml) was heated under reflux on a water-bath (60-70 °C) overnight. The excess carbon disulfide was removed under reduced pressure and the reaction mixture was then poured into ice-cold water and the obtained precipitate was collected by filtration, washed with water, dried and crystallized from dioxin-water (1:4) to give **7** (0.73 g, 61 %) as buff needles; m.p. 244-46 °C; Anal. Calcd. for $C_{17}H_{11}N_3OS$ (305); C, 66.88; H, 3.60; N, 13.77; S, 10.49. Found; C, 66.84; H, 3.76; N, 13.54; S, 10.72 %; IR (KBr, cm^{-1}): 3327 (NH), 3098 (CH) (Aromatic), 1600, 1585, 1472, 1453 (C=C) (Aromatic), 1340, 1242, 748; ^{1}H-NMR (400 MHz, DMSO-d_6, δ/ppm): 7.65-8.25 (9H, m, Ar-H), 8.45 (1H, s, pyridine-H), 11.23 (1H, s, NH); ^{13}C-NMR (100 MHz, DMSO-d_6, δ/ppm): 162.17, 157.12, 155.10, 148.41, 139.72, 129.20 (2C), 129.01 (3C), 127.63, 127.11 (3C), 126.61, 125.42, 120.13; MS (m/z, (relative abundance, %)): 305 (100), 304 (13), 275 (3), 263 (4), 245 (46), 244 (24), 229 (13), 217 (3), 204 (24), 190 (3), 176 (3), 94 (2), 93 (6), 75 (4), 51 (2), 43 (2).

*2-Phenylquinoline-4-carboxylic acid (mercapto-phenylamino-methylene)-hydrazide (**8**).*

A mixture of 2-phenyl-quinoline-4-carboxylic acid hydrazide **3** (1.09 g, 4 mmol) and phenyl isothiocyanate (0.54 g, 4 mmol) in absolute ethanol (20 ml) was heated under reflux for overnight. After cooling to room temperature, the reaction mixture was then poured into ice-cold water containing a few drops of acetic acid. The resulting precipitate was collected by filtration, washed with water and left to dry. Crystallization from diluted ethanol gave **8** (1.0 g, 63 %) as buff needles; m.p. 172-74 °C; Anal. Calcd. for $C_{23}H_{18}N_4OS$ (398); C, 69.34; H, 4.52; N, 14.07; S, 8.04. Found; C, 69.36; H, 4.66; N, 13.82; S, 8.23 %; IR (KBr, cm^{-1}): 3438, 3398, 3336 (NH), 3092, 3086, 3067 (CH) (Aromatic), 1671(C=O), 1605, 1582, 1458, 1444 (C=C) (Aromatic), 1350, 1165, 747; ^{1}H-NMR (400 MHz, DMSO-d_6, δ/ppm): 7.65-8.45 (10H, m, Ar-H; pyridine-H), 9.25(1H, s, NH),), 9.25 (1H, s, NH), 9.25 (1H, s, NH), 10.04 (1H, s, NH); ^{13}C-NMR (100 MHz, DMSO-d_6, δ/ppm): 172.12, 161.33, 156.71, 146.82, 142,51, 139.73, 139.42, 134.51, 132.80, 130.20, 129.0 (2C), 128.80 (2C), 127.10 (3C), 125.32 (2C), 124.52, 123.54, 121.33, 119.66; MS (m/z, (relative abundance, %)): 398 (13), 363 (25), 332 (68), 304 (37), 288 (41), 275 (4), 272 (11), 263 (48), 262 (100), 247 (28), 245 (15), 244 (13), 231 (43), 228 (91), 219 (11), 205 (16), 204 (85), 191 (3), 180 (8), 178 (3), 135 (29), 118 (11), 95 (3), 93 (2), 88 (32), 75 (23), 64 (11), 51 (10), 43 (5).

*General procedure for condensation of hydrazide **3** with aromatic aldehydes*

A mixture of 2-phenyl-quinoline-4-carboxylic acid hydrazide (**3**) (4 mmol) and appropriate aromatic aldehyde (4 mmol) was refluxed for 3h in absolute ethanol (20 ml) in the presence of 5 drops of piperidine. After completion, the reaction mixture was cooled to room temperature and filtered. The crude product was washed with water, dried and recrystallized from the proper solvent to give compounds **9a-e**. The yields and spectral data are given in the following.

*2-Phenylquinoline-4-carboxylic acid benzylidene-hydrazide (**9a**)*

White needles; 75%, m.p. 226-28 ºC (ethanol); Anal. Calcd. for $C_{23}H_{17}N_3O$ (351); C, 78.63; H, 4.84; N, 11.96. Found; C, 78.83; H, 4.79; N, 11.92 %; IR (KBr, cm^{-1}): 3238 (NH), 3102, 3094 (CH-Ar), 2964, 2804 (CH-Aliph), 1676 (C=O) (amide), 1594, 1564, 1485, 1442 (C=C) (Aromatic), 1325, 1142, 746; ^{1}H-NMR (400 MHz, DMSO-d_6, δ/ppm): 7.15 (1H, s, N=CH), 7.35-8.45 (11H, m, Ar-H), 12.55 (1H, s, NH); ^{13}C-NMR (100 MHz, DMSO-d_6, δ/ppm): 176.23, 158.77, 154.70, 146.81, 142.52, 139.73, 134.52, 132.81, 131.22, 130.82, 130.23, 129.00 (4C), 128.62 (2C), 127.11 (3C), 123.51, 121.32, 119.60; MS (m/z, (relative abundance, %)): 351 (11), 350 (21), 248 (24), 247 (39), 231 (43), 204 (100), 177 (3), 176 (5), 95 (3), 94 (6), 74 (4), 65 (3), 51 (2).

*2-Phenylquinoline-4-carboxylic acid (4-chloro-benzylidene-hydrazide) (**9b**)*

White needles; 70%, m.p. 232-34 ºC (dioxane/water (3:1)); Anal. Calcd. for $C_{23}H_{16}ClN_3O$ (385.5); C, 71.59; H, 4.15; Cl, 9.02; N, 10.89. Found; C, 71.75; H, 4.24; Cl, 8.73; N, 10.82 %; IR (KBr, cm^{-1}): 3233 (NH), 3057 (CH) (Aromatic), 1654 (C=O) (amide), 1590, 1490, 1470, 1445 (C=C) (Aromatic), 1345(C-N), 1082, 743; ^{1}H-NMR (400 MHz, DMSO-d_6, δ/ppm): 7.25-8.25 (14H, m, Ar-H; N=CH), 8.45 (1H, s, pyridine-H), 12.75 (1H, s, NH); MS (m/z, (relative abundance, %)): 386 (11), 385 (44), 384 (16), 248 (100), 231 (89), 205 (45), 204 (99), 203 (20), 177 (5), 137 (7), 117 (3), 93 (12), 74 (5), 64 (11), 51 (4).

*2-Phenylquinoline-4-carboxylic acid (2-methoxy-benzylidene)hydrazide (**9c**).*

White needles; 78%, m.p. 202-04 ºC (ethanol); Anal. Calcd. for $C_{24}H_{19}N_3O_2$ (381); C, 75.59; H, 4.98; N, 11.02. Found; C, 75.56; H, 4.86; N, 11.15 %; IR (KBr, cm^{-1}): 3281 (NH), 3098 (CH) (Aromatic), 2986 (CH) (alkyl), 1649 (C=O) (amide), 1600, 1585, 1495, 1455 (C=C) (Aromatic), 1342(C-N), 1245, 749; ^{1}H-NMR (400 MHz, DMSO-d_6, δ/ppm): 3.82 (3H, s, -OCH_3), 7.15-8.25 (14H, m, Ar-H), 8.35 (1H, s, pyridine-H), 8.85 (1H, s, N=CH), 11.78 (1H, s, NH); ^{13}C-NMR (100 MHz, DMSO-d_6, δ/ppm): 176.22, 162.54, 158.72, 154.71, 146.82, 142.54, 139.71, 134.50, 132.80, 131.81, 130.20 (2C), 129.00 (3C), 127.11 (2C), 123.5, 121.31, 119.62, 116.82, 56.30; MS (m/z, (relative abundance, %)): 381 (34), 380 (11), 262 (10), 248 (100), 247 (73), 231 (56), 206 (12), 205 (71), 204 (90), 203 (23), 176 (6), 119 (10), 94 (14), 86 (20), 84 (34), 75 (7), 74 (7), 58 (35), 51 (6), 43 (10).

*2-Phenylquinoline-4-carboxylic acid(4-nitro-benzylidene)hydrazide (**9d**).*

White needles; 86%, m.p. 282-84 ºC (dioxane/water (1:1)); Anal. Calcd. for $C_{23}H_{16}N_4O_3$ (396); C, 69.69; H, 4.04; N, 14.14. Found; C, 69.38; H, 3.84; N, 14.02 %; IR (KBr, cm^{-1}): 3285 (NH), 3098 (CH-Ar), 1659 (C=O) (amide), 1600, 1568, 1473, 1442 (C=C) (Aromatic), 1337, 1240, 748; ^{1}H-NMR (400 MHz, DMSO-d_6, δ/ppm): 7.55-8.55 (11H, m, Ar-H; pyridine-H; N=CH); 12.85 (1H, s, NH); ^{13}C-NMR (100 MHz, DMSO-d_6, δ/ppm): 174.20, 158.77, 154.65, 150.32, 146.31, 142.54, 139.77, 134.54, 132.82, 130.22, 129.90 (4C), 127.11 (3C), 123.70 (2C), 123.52, 121.32, 119.62; MS (m/z, (relative abundance, %)): 396 (14), 395 (3), 380 (8), 263 (4), 248 (27), 231 (65), 204 (100), 203 (16), 176 (9), 148 (3), 93 (10), 74 (5), 51 (5), 43 (8).

*2-Phenylquinoline-4-carboxylic acid(4-dimethylamino-benzylidine)hydrazide (**9e**).*

Yellow needles; 66%, m.p. 216-18 ºC (dioxane/water (1:2)); Anal. Calcd. for $C_{25}H_{22}N_4O$ (394); C, 76.14; H, 5.58; N, 14.21. Found; C, 76.20; H, 5.53; N, 14.16 %; IR (KBr, cm^{-1}): 3220(NH), 3096, 3082, 3067 (CH) (Aromatic), 2984, 2979 (CH) (alkyl), 1647 (C=O) (amide), 1593, 1484, 1470, 1440 (C=C) (Aromatic), 1325 (C-N), 743; ^{1}H-NMR (400 MHz, DMSO-d_6, δ/ppm): 2.89 (3H, s, -NCH_3), 7.15-8.45 (15H, m, Ar-H; pyridine-H; N=CH); 10.62 (1H, s, NH); ^{13}C-NMR (100 MHz, DMSO-d_6, δ/ppm): 173.40, 158.77, 154.72, 146.81 (2C), 142.52, 139.73, 134.56, 132.81, 130.22, 129.90 (2C), 129.11 (2C), 127.73, 127.10 (3C), 123.52, 121.31, 119.67, 113.22 (2C), 43.63 (2C); MS (m/z, (relative abundance, %)): 394 (100), 393 (11), 248 (34), 231 (36), 205 (28), 204 (98), 203 (16), 162 (57), 147 (21), 146 (98), 145 (11), 117 (8), 94 (7), 74 (7), 43 (8).

*4-[1,3,4-Oxadiazole-2-yl-2-phenyl-quinoline (**10**).*

A mixture of 2-phenyl-quinoline-4-carboxylic acid hydrazide **3** (1.09 g, 4 mmol), triethyl orthoformate (10 ml) and acetic anhydride (1 ml) was heated under reflux for 5h. Afterwards, the reaction mixture was cooled to room temperature and poured with stirring into ice-cold water. The resulting precipitate was collected, washed, dried and crystallized from ethanol gave **10** (0.58 g, 54 %) as yellow needles; m.p. 220-22 °C; Anal. Calcd. for $C_{17}H_{11}N_3O$ (273); C, 74.72; H, 4.02; N, 15.38. Found; C, 74.55; H, 4.07; N, 15.53 %; IR (KBr, cm^{-1}): 3098 (CH) (Aromatic), 1605, 1584, 1465, 1445 (C=C) (Aromatic), 1336 (C-N), 1225, 1082, 745; ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm):

7.55-8.45 (9H, m, Ar-H), 8.73 (1H, s, pyridine-H), 9.22 (1H, s, oxadiazole-H); MS (m/z, (relative abundance, %)): 273 (100), 272 (83), 248 (2), 245 (8), 231 (11), 228 (27), 217 (10), 205 (17), 204 (94), 189 (5), 105 (3), 94 (8), 74 (6), 64 (11), 51 (2).

*2-Phenylquinoline-4-carboxylic acid (2-oxo-1,2-dihydroindol-ylidene)hydrazide (**11**).*

A mixture of 2-phenyl-quinoline-4-carboxylic acid hydrazide **3** (1.09 g, 4 mmol) and isatin (4 mmol) in acetic acid (20 ml) was heated under for 5h. The reaction mixture was cool to room temperature and the obtained precipitate was collected by filtration, washed with water, dried and crystallized from ethanol to give **11** (1.0 g, 65 %) as orange crystals; m.p. 200-02 °C; Anal. Calcd. for $C_{24}H_{16}N_4O_2$ (392); C, 73.46; H, 4.08; N, 14.28. Found; C, 73.62; H, 4.12; N, 14.04 %; IR (KBr, cm^{-1}): 3323, 3285 (2NH), 3098 (CH) (Aromatic), 1659 (C=O) (isatin), 1647(C=O) (amide), 1604, 1590, 1480, 1447 (C=C) (Aromatic), 1325, 1283, 758; ^{1}H-NMR (400 MHz, DMSO-d_6, δ/ppm): 7.55-8.58 (14H, m, Ar-H; pyridine-H; N=CH), 11.35 (1H, s, NH), 12.15 (1H, s, NH); ^{13}C-NMR (100 MHz, DMSO-d_6, δ/ppm): 174.22, 163.14, 158.71, 155.34, 146.82, 142.54, 139.71, 138.76, 134.53, 132.81, 131.01, 130.22, 129.20 (3C), 127.10 (3C), 124.22, 123.52, 121.31 (2C), 120.52, 119.61; MS (m/z, (relative abundance, %)): 392 (12), 363 (8), 336 11(68), 304 (7), 292 (6), 250 (62), 231 (26), 205 (66), 204 (100), 203 (38), 177 (10), 149 (3), 147 (14), 132 (7), 119 (19), 117 (15), 95 (15), 93 (12), 87 (9), 75 (15), 74 (17), 60 (37), 51 (13), 45 (49), 43 (81).

*2-Phenylquinoline-4-carbonyl azide (**12**).*

A cold solution (0-5 °C) of sodium nitrite (0.31 g, 45 mmol) in 15 ml water was added to a suspension of the carbohydrazide **3** (1.09 g, 4 mmol) in HCl (20 ml, 50 %) in an ice bath (0-5 °C) over a period of 30 min. The reaction mixture was left to stir for 1 h at the same temperature and then poured into excess water. The yellow precipitate was filtered off, washed and air dried and kept without crystallization to give **12** (0.9 g, 82 %) of crude azide, m.p. 82-4 °C; Anal. Calcd. for $C_{16}H_{10}N_4O$ (274); C, 70.07; H, 3.64; N, 20.43. Found; C, 70.15; H, 3.44; N, 20.49 %; IR (KBr, cm^{-1}): 3097, 3086 (CH-Ar), 2143(CON_3), 1705 (C=O) (azide), 1600, 1590, 1475, 1449 (C=C) (Aromatic), 1333, 1275, 1065, 754; ^{1}H-NMR (400 MHz, DMSO-d_6, δ/ppm): 7.45-8.62 (10H, m, Ar-H; pyridine-H); ^{13}C-NMR (100 MHz, DMSO-d_6, δ/ppm): 188.12, 158.72, 146.42, 142.31, 139.72, 134.50, 132.81, 130.22, 129.00 (2C), 127.11 (3C), 123.54, 121.32, 119.62. MS (m/z, (relative abundance, %)): 274 (100), 232 (65), 204 (36), 197 (12), 182 (16), 164 (10), 56 (15), 43 (6).

*4-Phenyl-5-(2-phenylquinoline-4-yl)-4-H-[1,2,4]triazole-3-thiol (**13**).*

*A mixture of **8*** (1.6 g, 4 mmol) and a solution of NaOH (20 ml, 10%) was heated under for 3h. The reaction mixture was left to cool at room temperature and was neutralized with acetic acid. The obtained precipitate was collected by filtration, washed with water, dried and crystallized from DMF-water (3: 1) to give **13** (1.0 g, 68 %) as orange needles, m.p. 278-80 °C; Anal. Calcd. for $C_{23}H_{16}N_4S$ (380); C, 72.63; H, 4.21; N, 14.73; S, 8.42. Found; C, 72.52; H, 4.35; N, 14.77; S, 8.35 %; IR (KBr, cm^{-1}): 3108, 3096 (CH) (Aromatic), 2726 (SH), 1610, 1590, 1460, 1448 (C=C) (Aromatic), 1335, 1275, 1085, 755; ^{1}H-NMR (400 MHz, DMSO-d_6, δ/ppm): 7.3 8-8.57 (11H, m, Ar-H; pyridine-H), 10.85 (1H, s, NH); ^{13}C-NMR (100 MHz, DMSO-d_6, δ/ppm): 178.12, 157.78, 156.23, 148.42, 141.31, 139.72, 139.42, 129.23 (2C), 129.00 (2C), 128.83 (2C), 127.61, 127.11 (3C), 126.32, 125.31 (2C), 124.54, 122.32, 117.00; MS (m/z, (relative abundance, %)): 380 (100), 379 (9), 321 (3), 304 (6), 275 (3), 263 (2), 244 (9), 228 (11), 218 (17), 204 (7), 203 (3), 190 (3), 94 (2), 80 (1), 75 (9), 65 (1), 51 (2), 43 (1).

*Phenyl-[5-2-(phenylquinolin-4-yl)-[1,3,4]thiadiazol-2-yl]amine (**14**).*

A mixture of **8** (1.6 g, 4 mmol) and H_2SO_4 (10 ml, 98%) was stirred at room temperature for 3h. The reaction mixture was then poured into ice-cold water. The obtained precipitate was filtered off, washed with water, dried and crystallized from DMF-water (4: 1) to give **14** (1.0 g, 71 %) as orange crystals; m.p. 266-68 °C; Anal. Calcd. for $C_{23}H_{16}N_4S$ (380); C, 72.63; H, 4.21; N, 14.73; S, 8.42. Found; C, 72.74; H, 4.25; N, 14.62; S, 8.38%; IR (KBr, cm^{-1}): 3392 (NH), 3107 (CH) (Aromatic), 1595, 1565, 1455, 1442 (C=C) (Aromatic), 1340, 1274, 1075, 753; ^{1}H-NMR (400 MHz, DMSO-d_6, δ/ppm): 7.4 5-8.87 (15H, m, Ar-H; pyridine-H), 11.22 (1H, s, NH); MS (m/z, (relative abundance, %)): 380 (2), 350 (22), 263 (1), 248 (52), 231 (40), 228 (2), 204 (100), 178 (3), 1176 (5), 94 (6), 87 (3), 75 (3), 51 (2).

*(2-Phenylquinolin-4-yl)urea (**15**)*

A mixture of the azide **12** (1.09 g, 4 mmol) and water (15 ml) was heated under reflux for 1h. Afterwards, the solid precipitate that obtained after cooling to room temperature was collected by filtration, dried and crystallized from DMF-water (1: 3) to give **15** (0.72 g, 69 %) as pale yellow crystals; m.p. 231-33 °C; Anal. Calcd. for $C_{16}H_{13}N_3O$ (263); C, 73.00; H, 4.94; N, 15.96. Found; C, 72.84; H, 5.17; N, 15.78 %; IR (KBr, cm^{-1}): 3345-3280 (NH_2; NH), 3093, 3081 (CH) (Aromatic), 1648 (C=O) (amide), 1595, 1484, 1455, 1440 (C=C) (Aromatic), 1345 (C-N), 1280, 1075, 755; ^{1}H-NMR (400 MHz, DMSO-d_6, δ/ppm): 685 (2H, s, -NH_2), 7.35-8.35 (9H, m, Ar-H), 9.05 (1H, s, pyridine-H), 10.11 (1H, s, NH); ^{13}C-NMR (100 MHz, DMSO-d_6, δ/ppm): 158.12, 156.72, 150.91, 148.93, 139.77,

129.52, 129.02 (2C), 128.91, 127.11 (3C), 125.02, 120.30, 114.73, 103.11; MS (m/z, (relative abundance, %)): 264 (21), 263 (100), 247 (72), 219 (48), 214 (14), 205 (10), 190 (13), 180 (33), 165 (15), 142 (14), 57 (11), 42 (5).

*(2-Phenylquinolin-4-yl)carbamic acid ethyl ester (**16a**).*
A solution of the azide **12** (1.09 g, 4 mmol) in absolute ethanol (15 ml) was heated under reflux for 6 h. After cooling to room temperature, the reaction mixture was diluted with cold water (20 ml) and the separated product was filtered off, washed with water and dried. Crystallization from diluted ethanol gave carbamate **16a** (0.74 g, 64 %) as white needles; m.p. 82-4 °C; Anal. Calcd. for $C_{18}H_{16}N_2O_2$ (292); C, 73.97; H, 5.47; N, 9.58. Found; C, 73.92; H, 5.38; N, 9.77 %; IR (KBr, cm^{-1}): 3232(NH), 3097, 3086 (CH) (Aromatic), 1648 (C=O) (ester), 1600, 1580, 1477, 1443 (C=C) (Aromatic), 1345 (C-N), 1225, 1084, 758; ^{1}H-NMR (400 MHz, DMSO-d_6, δ/ppm): 1.28-1.45 (3H, t, -CH_2-CH_3), 4.18- 4.44 (2H, q, -CH_2-CH_3), 7.55- 8.52 (9H, m, Ar-H), 8.65 (1H, s, pyridine-H), 10.22 (1H, s, NH); ^{13}C-NMR (100 MHz, DMSO-d_6, δ/ppm): 157.98, 154.82, 150.91, 148.93, 139.71, 129.50, 129.01 (2C), 128.92, 127.11 (3C), 125.01, 120.30, 114.72, 103.11, 56.93, 13.37; MS (m/z, (relative abundance, %)): 293 (14), 292 (100), 277 (58), 263 (82), 248 (44), 215 (25), 210 (12), 205 (17), 191 (6), 182 (12), 165 (8), 57 (22), 42 (6).

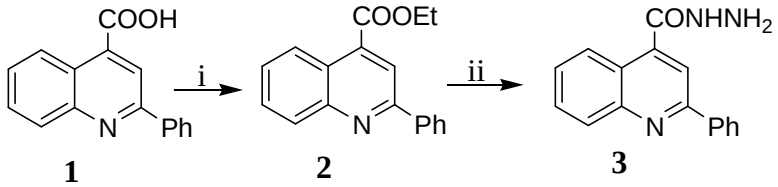
*(2-Phenylquinolin-4-yl)-carbamic acid butyl ester (**16b**).*
A mixture of the azide **12** (1.09 g, 4 mmol) and *n*-butanol (10 ml) was heated under reflux for 6h. The solid precipitate that was obtained after evaporation under reduced pressure and addition of water (20 ml) was filtered off and dried. Crystallization from CH_2Cl_2/PE 60-80°C (1: 4) gave carbamate **16b** (0.77 g, 61 %) as white needles; m.p. 144-46 °C; Anal. Calcd. for $C_{20}H_{20}N_2O_2$ (320); C, 75.00; H, 6.25; N, 8.75. Found; C, 75.21; H, 6.09; N, 8.62 %; IR (KBr, cm^{-1}): 3232 (NH), 3097, 3086 (CH) (Aromatic), 1648 (C=O) (ester), 1600, 1590, 1465, 1442 (C=C) (Aromatic), 1335 (C-N), 1225, 1074, 750; ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 0.95 (3H, t, CH_2CH_3), 1.33-1.78 (4H, m, CH_2-CH_2-), 4.21- 1.43 (3H, t, -CH_2-CH_2-), 7.52-8.25 (9H, m, Ar-H), 8.65 (1H, s, pyridine-H), 10.23 (1H, s, NH); ^{13}C-NMR (100 MHz, DMSO-d_6, δ/ppm): 159.23, 1455.82, 151.21, 148.92, 139.71, 129.52, 129.01 (2C), 128.91, 127.11 (3C), 125.02, 120.31, 114.72, 103.11, 63.82, 31.81, 19.33, 13.70; MS (m/z, (relative abundance, %)): 320 (94), 319 (92), 277 (2), 265 (2), 263 (9), 246 (100), 234 (2), 220 (53), 217 (5), 204 (11), 193 (2), 165 (2), 57 (12), 42 (4).

Antimicrobial Activity
The antimicrobial activity of 10 selected compounds was evaluated against 6 bacterial and 6 fungal strains. All microbial strains were kindly provided by the Assiut University Mycological Centre (AUMC). These strains are common contaminants of the environment in Egypt and some of which are involved in human and animal diseases (*Trichophyton rubrum, Candida albicans, Geotrichum candidum,S. brevicaulis, A.flavus*), plant diseases (F. oxy-sporum) or frequently reported from contaminated soil, water and food substances (*Escherichia coli, B. cereus, Pseudomonas aeruginosa, S. marcescens, S. aureus, M. luteus*).

To prepare *inoculate* for bioassay, bacterial strains were individually cultured for 48 h in 100 ml conical flasks containing 30 ml nutrient broth medium. Fungi were grown for 7 days in 100 ml conicals containing 30 ml Sabouraud's dextrose broth. Bioassay was done in 10 cm sterile plastic Petri plates in which microbial suspension (1 ml/plate) and 15 ml of appropriate agar medium (15 ml/plate) were poured. Nutrient agar and Sabouraud's dextrose agar were respectively used for bacteria and fungi. After solidification of the media, 5 mm diameter cavities were cut in the solidified agar (4 cavities/plate) using sterile cork borer. The tested compounds were dissolved in dimethyl sulfoxide (DMSO) at 2% w/v (¼20 mg/ml), pipetted and poured in the cavities (20 mL/cavity). Cultures were then incubated at 28 0C for 48 h in case of bacteria and up to 7 days in case of fungi. Results were read as the diameter (in mm) of inhibition zone around cavities. To determine the minimum inhibitory concentrations (MICs), several concentrations in DMSO, of the compounds under testing that gave positive results, have been prepared in descending manner down to a concentration of 0.02 mg/ml. The solutions of different compounds were similarly assayed as mentioned before and the least concentration (below which no activity was observed) was recorded as the MIC.

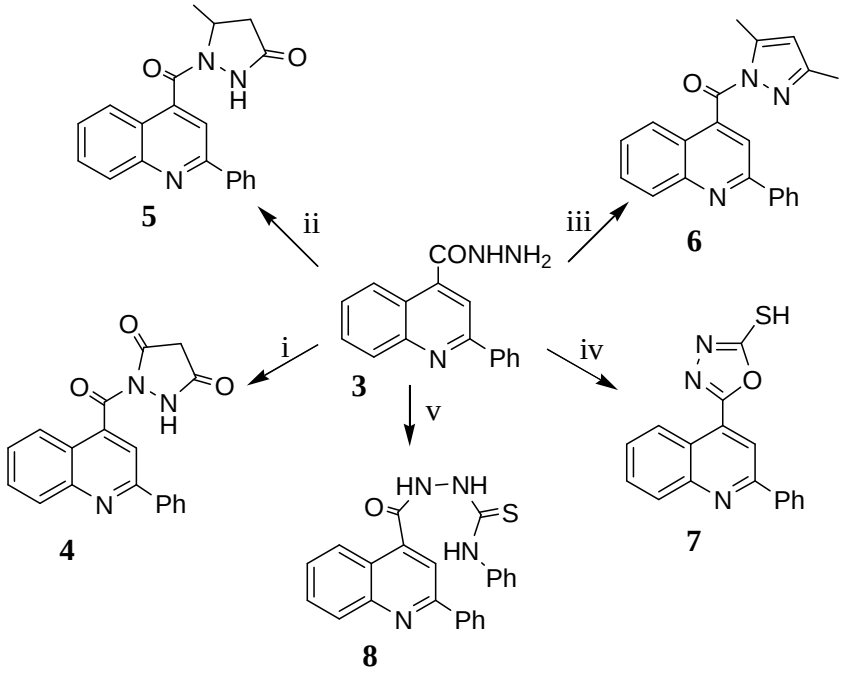
RESULTS AND DISCUSSION

Our first task was to synthesize the key intermediate 2-phenylquinoline-4-carbohydrazide **3** which in turn was achieved via two consecutive steps starting from atophan **1** as depicted in (Scheme 1). Thus, we first prepared the starting 2-phenylquinoline-4-carboxylic acid (**1**) following the literature [45] from the reaction of isatin and acetophenone in boiling ethanol in the presence of KOH in good yield. The acid **1** was esterified [46] by ethanol and H_2SO_4 gave the corresponding ethyl ester **2** followed by treatment with hydrazine in ethanol under reflux conditions to furnish carbohydrazide **3** [47].



Scheme 1. Reagents and conditions: (i) EtOH/HCl, reflux, 5 h, (ii) N_2H_4/EtOH, reflux, 4 h

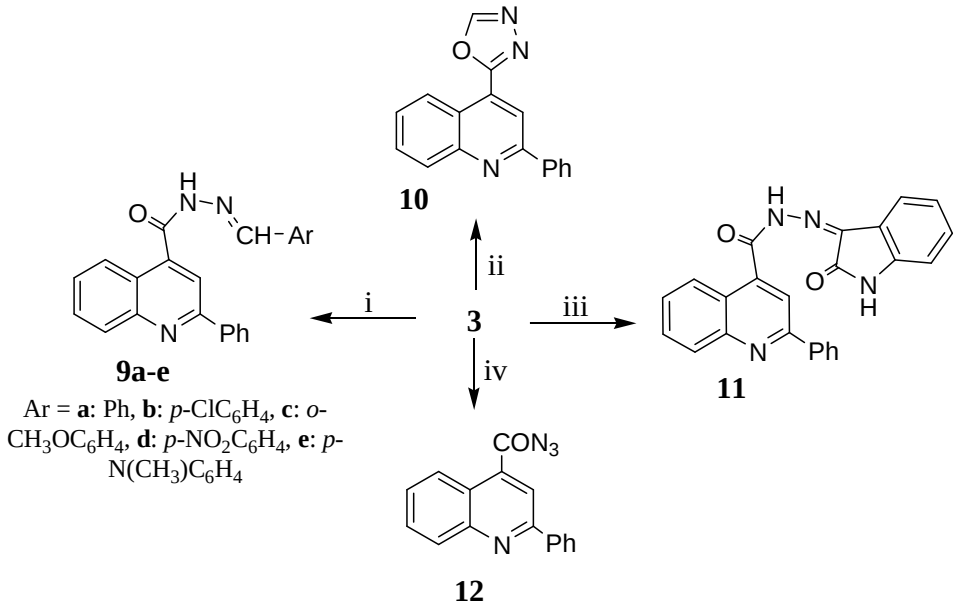
Several derivatives were obtained from the versatile compound **3**. Thus, **3** was reacted with some active methylene compounds such as diethyl malonate, ethyl acetoacetate and acetylacetone in refluxing acetic acid afforded 1-(2-phenyl-quinoline-4-carbonyl)-pyrazolidine-3,5-dione, 5-methyl-1-(2-phenyl-quinoline-carbonyl)-1,2-dihydro-pyrazol-3-one and (3,5-dimethyl-pyrazol-1-yl)-(2-phenyl-quinolin-4-yl)methanone (**4**-**6**) respectively (Scheme 2). Reaction of the carbohydrazide **3** with carbon disulfide in pyridine at 60-70 °C and with phenyl isothiocyanate in refluxing ethanol gave 5-(2-phenyl-quinolin-4-yl)-3*H*-[1,3,4]oxadiazole-2-thione (**7**) and 2-phenyl-quinoline-4-carboxylic acid (mercapto-phenylamino-methylene)-hydrazide (**8**) respectively.



Scheme 2. Reagents and conditions: (i) $CH_2(COOEt)_2$/AcOH, reflux, 12h, (ii) $CH_2(COCH_3)(COOEt)$/AcOH, reflux, 10h, (iii) $CH_2(COCH_3)_2$/AcOH, reflux, 10h, (iv) CS_2/Pridine, reflux, 60-70°C, 12 h, (v) PhNCS/EtOH, reflux, 15 h

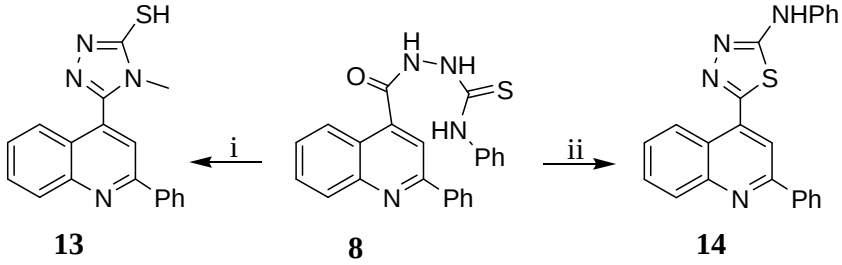
Condensation of the carbohydrazide **3** with some aromatic aldehydes, namely, benzaldeyde, 4-chlorobenzaldeyde, *o*-anisaldehyde, 4-nitrobenzaldehyde and 4-*N*,*N*-dimethylbenzaldehyde in refluxing ethanol containing catalytic amount of piperidine gave substituted benzylidine hydrazides **9a-e** respectively (Scheme 3).

The formation of 4-[1,3,4-oxadiazole-2-yl]-2-phenyl-quinoline (**10**) was achieved upon refluxing of the carbohydrazide **3** with triethylorthoformate in presence of acetic anhydride. The carbohydrazide **3** upon refluxing with isatin gave rise to the formation of 2-phenyl-quinoline-4-carboxylic acid (2-oxo-1,2-dihydro-indol-ylidene)-hydrazide (**11**). Treatment of carbohydrazide **3** with nitrous acid furnished the carboazide **12**.



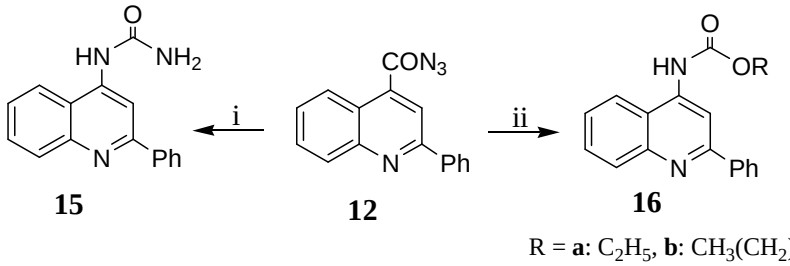
Scheme 3. Reagents and conditions: (i) ArCHO/Piperidine/EtOH, reflux, 3 h, (ii) $CH(OEt)_3/Ac_2O$, reflux, 5 h, (iii) Isatin/AcOH, reflux, 5 h, (iv) $NaNO_2$/HCl, 0 °C

2-Phenyl-quinoline-4-carboxylic acid(mercapto-phenylamino-methylene)-hydrazide (**8**) underwent cyclization by refluxing in NaOH to 4-phenyl-5-(2-phenyl-quinoline-4-yl)-4-*H*-[1,2,4]triazole-3-thiol (**13**) and upon stirring in concentrated sulfuric acid at room temperature to give phenyl-[5-2-(phenyl-quinolin-4-yl)-[1,3,4]thiadiazol-2-yl]amine (**14**) (Scheme 4).



Scheme 4. Reagents and conditions: (i) NaOH (10%), reflux, 3 h, (ii) H_2SO_4. 3 h, rt

Finally, refluxing of azide (**12**) in water, absolute ethanol and *n*-butanol give rise to the formation of (2-phenyl-quinolin-4-yl)-urea, (2-phenyl-quinolin-4-yl)-carbamic acid ethyl ester (**16a**) and (2-phenyl-quinolin-4-yl)-carbamic acid butyl ester (**15**), (**16a**) and (**16b**) respectively (Scheme 5).



Scheme 5. Reagents and conditions: (i) H_2O, reflux, 1 h, (ii) ROH, reflux, 6 h

Antimicrobial Activity

Using the agar well-diffusion method[48], ten selected derivatives (compounds **4**, **7**, **8**, **9b**, **9d**, **9e**, **11**, **12**, **16a**) were evaluated for their antibacterial and antifungal activities at Assiut University Mycological Center (AUMC). Thus, these compounds were screened against *Staphylococcus aureus* AUMC No. B-52, *Bacillus cereus* AUMC No. B-52, *Micrococcus luteus* AUMC No. B-112 as a Gram positive bacteria and *Escherichia coil* AUMC No. B-53,

Pseudomonas aeruginosa AUMC No. B-73 and *Serratia marcescens* AUMC No. B-55 as Gram negative bacteria were performed using chloramphenicol as control (Table 1).

Table 1. Antibacterial activity data [inhibition zone in mm/MICs (in mM)

Compound	*Staphylococcus aureus*	*Bacillus cereus*	*Micrococcs luteus*	*Escherichia coil*	*Pseudomonas aeruginosa*	*Serratia marcescens*
4	-	-	-	-	-	-
7	-	-	-	-	-	-
8	-	-	-	-	-	-
9b	-	-	-	-	-	-
9d	-	-	-	-	-	-
9e	-	-	-	-	-	-
11	-	-	-	-	-	-
12	8[a] (2.5)[b]	8 (2.5)	17 (20)	10 (5)	8 (2.5)	10 (10)
13	8 (10)	8 (5)	8 (2.5)	12 (10)	8 (1.25)	8 (2.5)
16a	-	-	-	-	-	-
CHL[c]	10 (0.08)	12 (1.25)	12 (2.5)	10 (0.08)	12 (0.3)	13 (1.25)

[a] p.i.= Partial Inhibition. [b]Diameter of the inhibition zone (mm) MIC (mM). The amount added in each pore is 50 µl. [c]CHL= Chloramphenicol

The MIC results indicated that two of the tested compounds (**12** and **13**) showed significant activity against *Staphylococcus aureus*, *Bacillus cereus*, *Micrococcus luteus*, *Escherichia coil* and *Pseudomonas aeruginosa* (Table 1). The rest of tested compounds were inactive against all bacterial strains used. The same compounds (**4, 7, 8, 9a, 9d, 9e, 11, 12** and **16a**) were screened for their antifungal activities against six fungal strains: (Candida albicans AUMC No. 418, *Trichophyton rubrum* AUMC No. 1804, *Aspergillus flavus* AUMC No. 1276, *Fusarium oxysporum* AUMC No. 5119, *Scopulariopsis brevicaulis* AUMC No. 729 and *Geotrichum candidum* AUMC No. 226) using clotrimazole as control. The results are listed in Table 2.

Table 2. Antifungal activity data [inhibition zone in mm/ MICs (in mM)

Compound	*C. albicans*	*G. candidm*	*F. oxysporum*	*S. brevicaylis*	*T. rubrum*	*A. flavus*
4	-	12[a] (20)[b]	-	-	-	-
7	-	-	10 (10)	-	-	-
8	-	-	-	-	18 (20)	-
9b	-	-	-	-	-	-
9d	-	-	-	-	-	-
9e	-	-	-	-	-	-
11	-	-	-	-	-	-
12	13 (20)	13 (20)	13 (5)	12 (5)	13 (20)	10 (5)
13	-	11(20)	13 (20)	12 (20)	24 (20)	-
16a	-	-	11 (10)	-	-	-
CLO[c]	12 (0.08)	14 (0.08)	14 (0.15)	24 (0.3)	35 (0.08)	15 (0.15)

[a] Partial Inhibition. [b]Diameter of the inhibition zone (mm) MIC (mM). The amount added in each pore is 50 µl. [c]CLO= Clotrimazole

The MIC values showed that compound **4** showed fair activity against *Geotrichum candidum* AUMC No. 226. Compound **8** showed moderate activity against *Trichophyton rubrum* AUMC No. 1804. Compound **12** showed good to moderate activity against *Fusarium oxysporum* AUMC No. 5119, *Scopulariopsis brevicaulis* AUMC No. 729, *Candida albicans* AUMC No. 418, *Geotrichum candidum* AUMC No. 226, *Trichophyton rubrum* AUMC No. 1804. Compound **7** and **16a** showed moderate activities against *Fusarium oxysporum* AUMC No. 5119. The rest of tested compounds were inactive against all fungal strains used (Table 2).

CONCLUSION

In conclusion, new atophans heterocycles were synthesized with good yields and their structure were determined and also assayed for their in vitro antifungal and antibacterial activity because the literature gives results enormously interesting on these subjects. The corresponding molecular structures were experimentally characterized by IR, ^{1}H-NMR, ^{13}C-NMR, MS and elemental analysis. Preliminary in-vitro tests for inhibition of certain compounds showed moderate activity of the new structures.

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