
Mohammed Y. Ebied¹, Wafaa A. Zaghary², Kamelia M. Amin¹, Sherif F. Hammad²,*

¹Pharmaceutical Chemistry Department, Faculty of Pharmacy, Cairo University, Cairo, Egypt.
²Pharmaceutical Chemistry Department, Faculty of Pharmacy, Helwan University, Ain Helwan, Cairo, Egypt.

*Corresponding author: Sherif F. Hammad, Pharmaceutical Chemistry Department, Faculty of Pharmacy, Helwan University, Ain Helwan, Cairo, Egypt. Tel.: +201013747382 Fax: +2022551601 E-mail address: sherifhammad2010@hotmail.com

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ABSTRACT

Objectives: The notable advancing in the medicinal chemistry arena against infectious diseases has resulted in the discovery of numerous valuable antimicrobial drugs that saved millions of lives throughout the last few decades. Nevertheless, the continuous reporting of multi-drug resistant strains of a number of diverse germs makes the need for novel broad-spectrum anti-infective agents still exists. Methods: Three series of ring-equivalent tricyclic benzo[h]quinazolines (compounds IIIa,b, IVa,b and Va,b), benzo[h]quinolines (compounds VIa-g, VIIa-c and VIIIa-c), and naphthaleno[d]thiazoles analogs (compounds X & XLa-e) were designed as bioisosteres and synthesized. Benzo[h]quinazolines were respectively obtained via treating chalcones IIa,b with urea, thiourea and guanidine carbonate in basic medium. The one-pot reactions of 6-methoxy-1-tetralone I with different aromatic aldehydes and active methylene-containing agents namely ethylcyanoacetate, malononitrile and thioenolactam in the presence of excess ammonium acetate afforded benzo[h]quinolines compounds VIa-g, VIIa-c and VIIIa-c respectively. Naphthaleno[d]thiazoles X & XLa-e were yielded upon cyclocondensation of the bromotetralone IX with thiourea and aldehydethiosemicarbazones. The chemical structures of the synthesized agents were elucidated based on their spectral data and elemental analyses. Results: The antimicrobial activity of some of the synthesized compounds was screened and only 2-bromo derivative IX and aminothiazole compound X exhibited broad antimicrobial effectiveness. The antifungal MIC value of X was 1.85 mg/mL. Conclusion: The new synthesized compounds, designed as bioisosteres, showed excellent potency against the tested gram (+) bacterial and fungal strains compared to reference drugs.

Keywords: Antimicrobial; Benzo[h]quinazolines; Benzo[h]quinolones; Naphthaleno[d]thiazoles

INTRODUCTION

Life threatening systemic infections continue to be a remarkably significant problem in healthcare. The microbial self-defense everlasting genetic mutations resulted in the elevated levels of multi-drug resistant strains of variable virulent pathogens and emerging of new infectious diseases. This issue is especially pronounced in immune-compromised and hospitalized patients and those under immune-suppressing therapy in organ transplantation and cancer treatment¹². In view of the drawbacks of many of the marketed antimicrobial agents and the high incidence of bacterial resistance to their activities, there is an urgently high demand for discovery of safer and more effective broad-spectrum agents. Among the substantial armories in the medicinal chemistry arsenal are the design and development of novel chemical entities of diverse mechanisms of actions to surmount any potential cross-resistance of the current medications³. Quinazoline nucleus is one of fused heterocyclic ring systems that possesses a wide array of biological activities. These pharmacological activities include DNA binding⁴, antitumor⁵⁻⁷, benzodiazepine and GABA receptor ligand activity⁸, antiviral⁹⁻¹⁰, antibacterial¹¹⁻¹², antituberculous¹²⁻¹³ and cellular phosphorylation and tyrosine kinase inhibition¹⁴. Many marketed drugs comprise quinazoline nucleus in their structures such as;
the α1-blocker alfuzocin, which is used in the treatment of BPH (benign prostate hyperplasia), the oral hypoglycemic balaglitazone, dacominib that is used in the treatment of non-small-cell lung carcinoma (in phase III clinical trials) and the broad-spectrum antifungal albacoza

15leole (Figure 1).

Similarly, quinoline condensed ring system has been found in a considerable number of pharmacologically active natural products and in clinically active drugs16-18. The broad diversity of pharmacological activities of quinoline-containing compounds includes antipsychotic19, anti-inflammatory 20,21, antioxidant 22, anti-HIV 23, antifungal 24, treatment of lupus25, treatment of neurodegenerative diseases26, anti-tubercular 27,28, antiprotozoal 29,30 and anticancer31,32. Among the marketed drugs carrying quinoline nucleus is the fluoroquinolone antibacterial ciprofloxacin. Most of the quinolone family members of drugs are the antimalarial chloroquine, the anti-retroviral saquinavir, the HMG-CoA reductase inhibitor pitavastatin and the farnesyltransferase inhibitor tipifarnib used for the treatment of leukemia 33 (Figure 2).

Moreover, benzothiazole fused heterocyclic scaffold has been reported to have a relatively variable pharmacological effects such as antimicrobial34, anticancer35,36, anti-inflammatory 37, β-2 adrenoceptor agonist and antidepressant activities38. Figure 3 depicts some of benzothiazole-containing drugs like; the sulfonamide diuretic ethoxozolmide, the antiviral and immuno-suppressive frentizole, the glutamate receptor antagonist riluzole used in treatment of amyotrophic lateral sclerosis, the anti-diabetic zopolrestat and the amyloid imaging agent thioflavin T38.

Driven by the urgent need to develop novel antimicrobial agents of broader spectrum of activity, more potency and less toxicity and in the shade of the aforementioned facts, we were interested in the synthesis of some structurally related congener tricycles of

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benzo[h]quinazolines, benzo[h]quinolines and naphthaleno[d]thiazoles. The designed isosteric tricycles were synthesized to rummage their potential synergistic antimicrobial activities.

**MATERIALS AND METHODS**

**Chemistry**

Melting points were determined on STUART scientific melting point apparatus and were uncorrected. The reactions times were determined using the thin layer chromatography (TLC) technique which was performed using plates of aluminum oxide coated with silica gel F 254 (Merck) neutral type and the eluent was chloroform/methanol (9:1). The organic solvents and extracts were dried with anhydrous Na$_2$SO$_4$ or anhydrous MgSO$_4$. The infrared (IR) spectra were recorded on Bruker FT-IR spectrophotometer as potassium bromide discs. Mass spectra (MS) were performed at 70 EV with Shimadzu GCMS, QP1000 EX using the Electron Ionization Technique (EI). The proton nuclear magnetic resonance ($^1$H-NMR) spectra were recorded in (DMSO-$d_6$ and CDCl$_3$) on Varian Gemini spectrophotometer at 200 MHz and Varian Mercury spectrophotometer at 300 MHz, using tetramethylsilan (TMS) as an internal reference and the chemical shift values (δ) are given in part per million (ppm). Elemental analysis were carried out at the Micro analytical Center, Cairo University. 6-Methoxy-1-tetralone I is commercially available.

![Figure 3](http://aprh.journals.ekb.eg/216-227)

**Figure 3.** Representative examples of marketed benzothiazole-containing Drugs

![Scheme 1](http://aprh.journals.ekb.eg/216-227)

**Scheme 1.** Synthesis of α,β-unsaturated ketones IIa-f, quinazolinones IIIa &b, quinazolinethiones VIa&b and iminioquazolines Va&b
General procedure for the synthesis of compounds IIa-f.

A mixture of 6-methoxy-1-tetralone (0.88 g, 0.005 mol), the appropriate aromatic aldehydes namely; p-chlorobenzaldehyde, 4-dimethylaminobenzaldehyde, 3,4-dimethoxy-benzaldehyde, p-nitrobenzaldehyde, and m-methoxybenzaldehyde (0.005 mol) in ethanol (30 mL) containing 10% NaOH (15 mL) was stirred at room temperature for 24 h. The formed precipitate was filtered and recrystallized from ethanol to give the desired compounds IIa-f.

- 2-(p-Chlorophenyl)methylene]-6-methoxy-3,4-dihydro-1(2H)-napthalenone (IIa): Yield (85%), mp 158-160°C; IR (KBr) δ max/(v. cm⁻¹): 3055 (CH=Ar), 2950, 2925 (CH-sp3), 1660 (C=O) and (1274, C-O); 1H NMR (CDCl₃, δ ppm): 2.91, (t, 2H, CH₂), 3.14 (t, 2H, CH₂), 3.93 (s, 3H, OCH₃), 6.71 (s, 1H, =CH₂), 6.80-8.22 (m, 7H, Ar-H); MS m/z (R.A.%): M⁺ 297 (100), [M+2]⁺ 299 (43), 270 (18.8); Anal. Calcd. For C₁₆H₁₃ClO₂ (298.77); C, 72.69; H, 5.06. Found: C, 72.69; H, 5.06%.

- 2-(p-Chlorophenyl)methylene]-6-methoxy-3,4-dihydro-1(2H)-napthalenone (IIb): Yield (70%), mp 43-45°C; IR (KBr) δ max/(v. cm⁻¹): 3067 (CH=Ar), 2942, 2927 (CH-sp3), 1637 (C=O) and (1245, C-O); MS m/z (R.A.%): M⁺ 308 (100); Anal. Calcd. For C₁₆H₁₃ClO₂ (307.39); C, 78.15; H, 6.89; N, 4.56. Found: C, 78.20; H, 6.70; N, 4.52%.

- 2-(3,4-Dimethoxyphenyl)methylene]-6-methoxy-3,4-dihydro-1(2H)-napthalenone (IIc): Yield (75%), mp 98-100°C; IR (KBr) δ max/(v. cm⁻¹): 3088 (CH=Ar), 2961, 2927 (CH-sp3), 1654 (C=O) and (1250, C-O); Anal. Calcd. For C₂₀H₂₀O₄ (324.37); C, 74.06; H, 6.22. Found: C, 74.23; H, 6.30%.

- 2-[Cinnamomethylene]-6-methoxy-3,4-dihydro-1(2H)-napthalenone (IID): Yield (85%), mp 138-140°C; MS m/z (R.A.%): M⁺ 290 (100); Anal. Calcd. For C₁₆H₁₂O₂ (290.36); C, 82.73; H, 6.25; Found: C, 83.10; H, 6.31%.

- 2-[p-Nitrophenyl)methylene]-6-methoxy-3,4-dihydro-1(2H)-napthalenone (IIe): Yield (90%), mp 168-170°C; IR (KBr) δ max/(v. cm⁻¹): 3092 (CH=Ar), 2934 (CH-sp3), 1663 (C=O), 1514 (NO₂, asymmetric), 1342 (NO₂, symmetric) and (1270, C-O); MS m/z (R.A.%): M⁺ 308 (100); Anal. Calcd. For C₁₆H₁₂NO₄ (309.32); C, 69.89; H, 4.89; N, 4.53. Found: C, 69.45; H, 4.90; N, 4.90%.

- 2-[3-Methoxyphenyl)methylene]-6-methoxy-3,4-dihydro-1(2H)-napthalene one (IIf): Yield (80%), mp 78-80°C; IR (KBr) δ max/(v. cm⁻¹): 3055 (CH=Ar), 2950, 2925 (CH-sp3), 1659 (C=O) and (1255, C-O); 1H NMR (CDCl₃, δ ppm): 2.91 (t, 2H, CH₂), 3.14 (t, 2H, CH₂), 3.86 (s, 3H, OCH₃), 3.95 (s, 3H, OCH₃), 6.71 (s, 1H, =CH₂), 6.89-8.25 (m, 7H, Ar-H); Anal. Calcd. For C₁₆H₁₄O₃ (294.35); C, 77.53; H, 6.16. Found: C, 77.63; H, 6.25.

General procedure for the synthesis of quinazolines IIIa&b, IVa&b and Vaa&b

An alcoholic solution of urea, thiourea or guanidine carbonate (0.01 mol) in absolute ethanol (10 mL) was added to a mixture of the appropriate chalcones IIa and/or IIb (0.01 mol), potassium hydroxide (1.12g, 0.02 mol) in absolute ethanol (30 mL). The reaction
mixture was allowed to reflux for 6 h and the solvent was removed under reduced pressure. The separated residue was washed with water and crystallized from ethanol.

- 4-(4-Chlorophenyl)-8-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[\(h\)]quinazoline (IIIa): Yield (40%), mp 158-160°C; IR(KBr) \(\delta\) max/(v. cm\(^{-1}\))): 3340 (NH), 3050 (CH-Ar), 2944 (CH-sp3), 1659 (C=O) and (1273, C-O); \(^1\)H NMR (DMSO-d\(_6\), \(\delta\) ppm): 2.90 (t, 2H, CH\(_2\)), 3.13 (t, 2H, CH\(_2\)), 3.91 (s, 3H, OCH\(_3\)), 6.81-8.20 (m, 7H, Ar-H), 9.34 (s, 1H, NH), D,O exchangeable; MS m/z (R.A.%) : M\(^+\) 339 (28), [M+2\(^+\)] 341 (9); Anal. Calcd. For C\(_{19}\)H\(_{13}\)ClN\(_2\)O\(_2\) (338.79): C, 67.36; H, 4.46; N, 8.27; Found: C, 67.20; H, 4.40; N, 8.87%.

- 4-(4-Dimethylaminophenyl)-8-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[\(h\)]quinazoline (IIIb): Yield (50%), mp 167-170°C; IR(KBr) \(\delta\) max/(v. cm\(^{-1}\))): 3344 (NH), 3192 (CH-Ar), 2937 (CH-aliphatic), 1668 (C=O) and (1274, C-O); MS m/z (R.A.%) : M\(^+\) 348 (100); Anal. Calcd. For C\(_{21}\)H\(_{15}\)N\(_2\)O\(_2\) (347.42): C, 72.60; H, 6.09; N, 12.10; Found: C, 72.32; H, 5.55; N, 11.85%.

- 4-(4-Chlorophenyl)-8-methoxy-2-thioxo-1,2,5,6-tetrahydrobenzo[\(h\)]quinazoline (IVa): Yield (50%), mp 238-240°C; IR(KBr) \(\delta\) max/(v. cm\(^{-1}\))): 3271 (NH), 3108 (CH-Ar), 2926 (CH-sp3), 1295 (C=S) and (1248, C-O); \(^1\)H NMR (CDCl\(_3\), \(\delta\) ppm): 2.91 (t, 2H, CH\(_2\)), 3.11 (t, 2H, CH\(_2\)), 3.94 (s, 3H, OCH\(_3\)), 6.71-8.25 (m, 7H, Ar-H), 9.42 (s, 1H, NH), D,O exchangeable; MS m/z (R.A.%) : M\(^+\) 339 (28), [M+2\(^+\)] 341 (10); Anal. Calcd. For C\(_{19}\)H\(_{15}\)ClN\(_2\)O\(_2\) (354.87): C, 64.30; H, 4.26; N, 7.89; Found: C, 63.88; H, 4.35; N, 7.50%.

- 4-(4-Dimethylaminophenyl)-8-methoxy-2-thioxo-1,2,5,6-tetrahydrobenzo[\(h\)]quinazoline (IVb): Yield (53%), mp 260-262°C; IR(KBr) \(\delta\) max/(v. cm\(^{-1}\))): 3346 (NH), 3188 (CH-Ar), 2951 (CH-sp3), 1604 (C=N) and (1249, C-O); MS m/z (R.A.%) : M\(^+\) 337 (100), [M+2\(^+\)] 339 (34); Anal. Calcd. For C\(_{20}\)H\(_{17}\)ClN\(_2\)O\(_2\) (337.82): C, 67.55; H, 4.77; N, 12.44; Found: C, 67.74; H, 5.00; N, 12.57%.

- 4-(4-Dimethylaminophenyl)-8-methoxy-2-imino-1,2,5,6-tetrahydrobenzo[\(h\)]quinazolines (Va): Yield (53%), mp 262-264°C; IR(KBr) \(\delta\) max/(v. cm\(^{-1}\))): 3346 (NH), 3188 (CH-Ar), 2951 (CH-sp3), 1604 (C=N) and (1249, C-O); \(^1\)H NMR (CDCl\(_3\), \(\delta\) ppm): 2.92 (t, 2H, CH\(_2\)), 3.0 (t, 2H, CH\(_2\)), 3.11 (s, 6H, N(CH\(_3\))\(_2\)), 3.95 (s, 3H, OCH\(_3\)), 6.71-8.17 (m, 7H, Ar-H), 9.42, 9.71 (2s, 2H, 2NH, D,O exchangeable); MS m/z (R.A.%) : M\(^+\) 345 (98.8); Anal. Calcd. For C\(_{21}\)H\(_{17}\)ClN\(_2\)O\(_2\) (346.43): C, 72.81; H, 6.40; N, 16.17; Found: C, 72.80; H, 6.20; N, 16.16%. (m, 7H, Ar-H), 9.42 (s, 1H, NH), D,O exchangeable); MS m/z (R.A.%) : M\(^+\) 339 (28), [M+2\(^+\)] 341 (10); Anal. Calcd. For C\(_{19}\)H\(_{13}\)ClN\(_2\)O\(_2\) (354.87): C, 64.30; H, 4.26; N, 7.89; Found: C, 63.88; H, 4.35; N, 7.50%.

Reagents and conditions: (i) Br\(_2\), Glacial AcOH, rt, (70%); (ii) thiourea, absolute EtOH, reflux, (80%); (iii) thiosemicarbazones, DMF, reflux, (65-80%).

**Scheme 3.** Synthesis of 4,5-dihyronaphtho[1,2-d]thiazoles X and XIa-e.

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4-(4-Dimethylaminophenyl)-8-methoxy-2-thioxo-1,2,5,6-tetrahydrobenzo[h]quinazoline (IVb): Yield (53%), mp 162-164°C; IR(KBr) δ max/(v. cm⁻¹): 3346 (NH), 3188 (CH-Ar), 2951 (CH-sp3), 1604 (C=N) and (1249, C-0); MS m/z (R.A.%): M⁺ 337 (100), [M+2]⁺ 339 (34); Anal. Calcd. For C₁₂H₁₀ClN₂O (337.82); C, 67.55; H, 4.77; N, 12.44; Found: C, 67.74; H, 5.00; N, 12.57.

4-(4-Chlorophenyl)-8-methoxy-2-imino-1,2,5,6-tetrahydrobenzo[h]quinazolines (Va): Yield (53%), mp 190-192°C; IR(KBr) δ max/(v. cm⁻¹): 3270 (NH), 3010 (CH-Ar), 2920 (CH-sp3), 1294 (C=S) and (1248, C-0); MS m/z (R.A.%): M⁺ 363 (44); Anal. Calcd. For C₁₃H₁₂N₂O₅ (363.48); C, 69.39; H, 5.82; N, 11.56; Found: C, 69.32; H, 5.35; N, 11.53.

General procedure for the synthesis of quinolines VIa-g

A mixture of 6-methoxy-1-tetralone (1.78 g, 0.01mol), ethylcyanoacetate (1.2 g, 0.01mol), the appropriate aromatic aldehydes namely; p-chlorobenzaldehyde, 4-Dimethylbenzaldehyde, 3,4-dimethoxybenzaldehyde, cinnaamaldehyde, p-nitrobenzaldehyde, m-methoxybenzaldehyde and salicylaldehyde (0.01mol) and of ammonium acetate (6.1 g, 0.08 mol) in n-butanol (40 mL) was heated under reflux for 5 h. The formed precipitate was filtered under suction, washed with water and with petroleum ether and crystallized form acetic acid to give the corresponding pyridines VIa-g.

4-(4-Chlorophenyl)-8-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[h]quinoline-3-carbonitrile (VIIa): Yield (78%), mp 260-262°C; IR(KBr) δ max/(v. cm⁻¹): 3270 (NH), 3082 (CH-Ar), 2930 (CH-sp3), 2219 (CN), 1635 (C=O) and (1257, C-O); 1H NMR (CDCl₃, δ ppm): 2.42 (t, 2H, CH₂), 2.81 (t, 2H, CH₂), 3.91 (s, 3H, OCH₃), 7.03-8.15 (m, 7H, Ar-H), 9.46 (s, 1H, NH, D₂O exchangeable); MS m/z (R.A.%): M⁺ 364 (100), [M+2]⁺ 366 (38); Anal. Calcd. For C₁₃H₁₁ClN₂O₂ (362.81); C, 69.52; H, 4.17; N, 7.72; Found: C, 69.80; H, 4.30; N, 7.86%.

4-(4-Dimethylaminophenyl)-8-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[h]quinoline-3-carbonitrile (VIIb): Yield (74%), mp 260-262°C; IR(KBr) δ max/(v. cm⁻¹): 3450 (NH), 3125 (CH-Ar), 2913 (CH-sp3), 2212 (CN), 1670 (C=O) and (1257, C-O); Anal. Calcd. For C₁₃H₁₁N₂O₂ (371.45); C, 74.37; H, 5.70; N, 11.32; Found: C, 74.76; H, 6.12; N, 11.22%.

4-(3,4-Dimethoxyphenyl)-8-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[h]quinoline-3-carbonitrile (VIIc): Yield (80%), mp >300°C; IR(KBr) δ max/(v. cm⁻¹): 3284 (NH), 3075 (CH-Ar), 2940 (CH-sp3), 2224 (CN), 1715 (C=O) and (1251, C-O); MS m/z (R.A.%): M⁺ 388 (100); Anal. Calcd. For C₁₃H₁₂N₂O₄ (388.42); C, 71.12; H, 5.19; N, 7.21; Found: C, 71.58; H, 5.14; N, 7.25%.

4-(Cinnamyl)-8-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[h]quinoline-3-carbonitrile (VIId): Yield (75%), mp 290-292°C; IR(KBr) δ max/(v. cm⁻¹): 3281 (NH), 3079 (CH-Ar), 2933 (CH-sp3), 2219 (CN), 1629 (C=O) and (1253, C-O); 1H NMR (CDCl₃, δ ppm): 2.72 (t, 2H, CH₂), 2.93 (t, 2H, CH₂), 3.95 (s, 3H, OCH₃), 7.01 (d, 1H, -CH=), 7.12 (d, 1H, -CH=), 7.31-8.24 (m, 8H, Ar-H), 9.41 (s, 1H, NH, D₂O exchangeable); Anal. Calcd. For C₁₅H₁₃N₂O₄ (354.41); C, 77.95; H, 5.12; N, 7.91; Found: C, 77.63; H, 5.30; N, 8.17%.

4-(4-Nitrophenyl)-8-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[h]quinoline-3-carbonitrile (VIIe): Yield (82%), mp 240-242°C; IR(KBr) δ max/(v. cm⁻¹): 3419 (NH), 3135 (CH-Ar), 2924 (CH-sp3), 2217 (CN), 1640 (C=O), 1535 (NO₂, asymmetric), 1349 (NO₂ sym.) and (1250, C-O); Anal. Calcd. For C₁₅H₁₂N₂O₄ (373.37); C, 67.55; H, 4.05; N, 11.26; Found: C, 67.62; H, 4.27; N, 11.76%.

4-(4-Methoxyphenyl)-8-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[h]quinolono-3-carbonitrile (VIIf): Yield (85%), mp 278-280°C; IR(KBr) δ max/(v. cm⁻¹): 3287 (NH), 3085 (CH-Ar), 2950 (CH-sp3), 2219 (CN), 1705 (C=O) and (1250, C-O); MS m/z (R.A.%): M⁺ 358 (100); Anal. Calcd. For C₁₅H₁₃N₂O₃ (358.40); C, 73.73; H, 5.06; N, 7.82; Found: C, 73.40; H, 4.70; N, 8.16%.

4-(2-Hydroxyphenyl)-8-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[h]quinolinone-3-carbonitrile (VIIg): Yield (70%), mp 258-260°C; IR(KBr) δ max/(v. cm⁻¹): 3482 (OH), 3288 (NH), 3095 (CH-Ar), 2940 (CH-sp3), 2218 (CN), 1705 (C=O) and (1259, C-O); Anal. Calcd. For C₁₅H₁₄N₂O₃ (344.37); C, 73.24; H, 4.68; N, 8.14; Found: C, 73.14; H, 4.56; N, 8.25%.

General procedure for the synthesis of quinolines VIIa-c

A mixture of 6-methoxy-1-tetralone (1.78 g, 0.01mol), the appropriate aromatic aldehydes namely; p-chlorobenzaldehyde, p-dimethylaminobenzaldehyde and 3,4-dimethoxybenzaldehyde (0.01 mol), of thioycanoacetamide (1 g, 0.01 mol) and ammonium acetate (0.75 g, 0.015 mol) in ethyl alcohol (30 mL) was refluxed for 2-10 h. The resulting product was filtered and recrystallized from ethanol to give the corresponding compounds VIIa-c.
4-(4-Chlorophenyl)-8-methoxy-2-thioxo-1,2,5,6-tetrahydrobenzo[h]quinolone-3-carbonitrile (VIIa): Yield (72%), mp 105-107°C; IR (KBr) δ max (v. cm⁻¹): 3360 (NH), 3142 (CH-Ar), 2942 (CH-sp3), 2209 (CN), 1347 (C=S) and (1251, C-O); MS m/z (R.A.%): M⁺ 377 (10), [M+2]⁺ 379 (3); Anal. Calcd. For C₂₁H₁₈ClN₂O₂ (378. 87): C, 66.56; H, 3.99; N, 7.39; Found: C, 66.91; H, 4.46; N, 7.25%.

4-(4-Dimethylaminophenyl)-8-methoxy-2-thioxo-1,2,5,6-tetrahydrobenzo[h]quinolone-3-carbonitrile (VIIb): Yield (70%), mp 208-210°C; IR (KBr) δ max (v. cm⁻¹): 3388 (NH), 3060 (CH-Ar), 2929 (CH-sp3), 2208 (CN), 1371 (C=S) and (1256, C-O); Anal. Calcd. For C₂₃H₂₁N₂O₂ (387.50): C, 71.29; H, 5.46; N, 10.84; Found: C, 71.27; H, 5.05; N, 10.38%.

4-(3,4-Dimethylthiosemicarbazonyl)-8-methoxy-2-thioxo-1,2,5,6-tetrahydrobenzo[h]quinolone-3-carbonitrile (VIIc): Yield (75%), mp 268-270°C; IR (KBr) δ max (v. cm⁻¹): 3448 (NH), 3060 (CH-Ar), 2935 (CH-sp3), 2215 (CN), 1373 (C=S) and (1258, C-O); ¹H NMR (CDCl₃, δ ppm): 2.81 (s, 4H, (CH₂)), 3.86 (s, 3H, OCH₃), 3.95 (s, 3H, OCH₃), 4.01 (s, 3H, OCH₃), 6.71-8.13 (m, 6H, Ar-H), 9.41 (s, 1H, NH, D₂O exchangeable); Anal. Calcd. For C₂₃H₂₉N₂O₂S (404. 48): C, 68.29; H, 4.98; N, 6.93; Found: C, 68.61; H, 4.71; N, 6.74%.

General procedure for the synthesis of quinolines VIIIa-c
A mixture of 6-methoxy-1-tetralone I (1.76 g, 0.01 mol), the appropriate aromatic aldehydes namely, p-chlorobenzaldehyde, 4-dimethylaminobenzaldehyde and 3,4-dimethoxybenzaldehyde (0.01 mol), malononitrile (0.66 g, 0.01 mol) and ammonium acetate (6.2 g, 0.08mol) in absolute ethanol (50 mL) was refluxed for 6-10 h. The reaction mixture was concentrated and the separated precipitate was filtered under suction and washed with water. Recrystallization from ethanol gave the corresponding derivatives VIIIa-c.

4-(4-Chlorophenyl)-8-methoxy-2-imino-1,2,5,6-tetrahydrobenzo[h]quinoline-3-carbonitrile (VIIIa): Yield (65%), mp 203-205 °C; IR (KBr) δ max (v. cm⁻¹): 3453 (NH, asymmetric), 3353 (NH, sym), 3089 (CH-Ar), 2939 (CH-sp3), 2212 (CN), and 1248 (C-O); MS m/z (R.A.%): M⁺ 361 (100), [M+2]⁺ 363 (37); Anal. Calcd. For C₂₁H₁₉ClN₂O (361.84): C, 69.71; H, 4.46; N, 11.61; Found: C, 69.92; H, 4.42; N, 11.33%.

4-(4-Dimethylaminophenyl)-8-methoxy-2-imino-1,2,5,6-tetrahydrobenzo[h]quinoline-3-carbonitrile (VIIIb): Yield (70%), mp 178-180°C; IR (KBr) δ max (v. cm⁻¹): 3459 (NH, asymmetric), 3357 (NH, sym), 3088 (CH-Ar), 2938 (CH-sp3), 2212 (CN), and 1248 (C-O); ¹H NMR (CDCl₃, δ ppm): 2.82 (s, 4H, (CH₂)), 3.11 (s, 6H, N(CH₃)), 3.93 (s, 3H, OCH₃), 6.72-8.11 (m, 7H, Ar-H), 9.46, 9.61 (2s, 2H, NH, D₂O exchangeable); MS m/z (R.A.%): M⁺ 370 (100); Anal. Calcd. For C₂₃H₂₉N₂O (370.46): C, 74.57; H, 5.99; N, 15.13; Found: C, 74.50; H, 6.30; N, 15.42%.

4-(3,4-Dimethyloxazolyl)-8-methoxy-2-imino-1,2,5,6-tetrahydrobenzo[h]quinolone-3-carbonitrile (VIIIc): Yield (68%), mp 170-172°C; IR (KBr) δ max (v. cm⁻¹): 3475 (NH, asymmetric), 3361 (NH, sym), 3085 (CH-Ar), 2944 (CH-sp3), 2203 (CN), and 1263 (C-O); Anal. Calcd. For C₂₃H₂₉N₂O (387.44): C, 71.30; H, 5.46; N, 10.85; Found: C, 71.74; H, 5.61; N, 10.31%.

2-Bromo-6-methoxy-1-tetralone (IX): A mixture of 6-methoxy-1-tetralone I (0.88gm, 0.005 mol) and bromine (0.2 ml, 0.005 mol) in glacial acetic acid (30 mL) was stirred at room temperature for 5 h, then poured onto a mixture of crushed ice. The precipitated mass was filtered and crystallized from ethyl alcohol to give IX. Yield (70%), mp 65-67°C; IR (KBr) δ max (v. cm⁻¹): 3058 (CH-Ar), 2934 (CH-sp3), 1672 (C=O), and 1263 (C-O); MS m/z (R.A.%): M⁺ 254 (14.44), [M+2]⁺ 256 (14.88); Anal. Calcd. For C₁₁H₁₂BrO₂ (255.11): C, 51.79; H, 4.35; Found: C, 51.56; H, 4.63%.

7-Methoxy-4,5-diiodophenanthro[1,2-d][1,2-d][thiazol-2-amine] (X). A mixture of IX (2.5g, 0.01 mol) and thiourea (0.76 g, 0.01 mol) was refluxed in ethyl alcohol (30 mL) for 4 h. The formed precipitate was filtered by suction and recrystallized from glacial acetic acid to give the compound X. Yield (80%), mp 263-265°C; IR (KBr) δ max (v. cm⁻¹): 3254 (NH), 3064 (CH-Ar), 2972 (CH-sp3), 1633 (C=N), and 1248 (C-O); ¹H NMR (DMSO-d₆, δ ppm): 2.72 (t, 2H, CH₂), 2.91 (t, 2H, CH₂), 3.9 (s, 3H, OCH₃), 4.56 (s, 2H, NH₂, D₂O exchangeable), 6.91-8.12 (m, 3H, Ar-H); MS m/z (R.A.%): M⁺ 232 (100); Anal. Calcd. For C₁₂H₁₂N₂O₂ (232.32): C, 62.04; H, 5.21; N, 12.06; Found: C, 62.21; H, 5.48; N, 12.04%.

General procedure for the synthesis of N-(Substituted benzylidene)-N’-(7-methoxy-4,5-diiodophenanthro[1,2-d][1,2-d][thiazol-2-yl]hydrazines (Xla-e).
A mixture of the compound IX (2.54 g, 0.01 mol), the appropriate thiosemicarbazone namely: p-chlorobenzaldehydethiosemicarbazone, p-dimethyl amino- benzaldehydethiosemicarbazone, 3,4-dimethoxy benzaldehydethiosemicarbazone, cinnamaldehydethiosemicarbazone, p-nitrobenzaldehydethiosemicarbazone (0.01 mol) in DMF (30 mL) was refluxed for 5-10 h. Then, the reaction mixture was cooled and poured onto ice water. The precipitate was filtered under suction and crystallized from DMF /water to give the corresponding derivatives Xla-e.

2-(4-Chlorophenyl)methylenehydrazino]-7-methoxy-4,5-diiodophenanthral[2,1-d][thiazole (Xla): Yield (75%), mp 170-172°C; IR (KBr) δ max (v. cm⁻¹): 3421 (NH), 3060 (CH-Ar), 2925 (CH-sp3), 1623 (C=N), and 1247 (C-O); MS m/z (R.A.%): M⁺ 369 (14.44), 229 (100); Anal. Calcd. For C₁₉H₁₆ClN₃O₆ exchangeable).
(369.89); C, 61.70; H, 4.36; N, 11.36, Found: C, 61.71; H, 4.92; N, 11.54%.

- 2-[(4-Dimethylaminophenyl)methylene hydrazino]-7-methoxy-4,5-dihydroanthaleno [d]thiazole (XIIb): Yield (80%), mp 116-118°C; IR (KBr) δ max/(v. cm⁻¹): 3378 (NH), 3060 (CH=Ar), 2891 (CH-sp), 1605 (C=N) and 1248 (C-O); Anal. Calcd. For C₂₁H₁₃N₂O₃ (378.49): C, 66.64; H, 5.86; N, 14.80, Found: C, 66.58; H, 5.69; N, 14.36%.

- 2-[(3,4-Dimethoxyphenyl)methylene hydrazino]-7-methoxy-4,5-dihydroanthaleno[d] thiazole (XIIc): Yield (65%), mp 204-206°C; IR (KBr) δ max/(v. cm⁻¹): 3402 (NH), 3073 (CH=Ar), 2936 (CH-sp), 1624 (C=N) and 1256 (C-O); Anal. Calcd. For C₂₁H₁₉N₂O₄S (395.48): 63.78; H, 5.35; N, 10.86%.

- 2-[(Cinnamyl)methylenehydrazino]-7-methoxy-4,5-dihydroanthaleno[d] thiazole (XIId): Yield (74%), mp 180-182°C; IR (KBr) δ max/(v. cm⁻¹): 3381 (NH), 3045 (CH=Ar), 2931 (CH-sp), 1610 (C=N) and 1247 (C-O); ¹H NMR (CDCl₃, δ ppm): 2.91 (t, 2H, CH=), 7.22 (m, 7H, -CH=), 7.23-8.24 (m, 8H, Ar-H), 9.40 (s, 1H, NH, D₂O exchangeable); Anal. Calcd. For C₂₁H₁₃N₂O₃ (361.48): C, 69.78; H, 5.29; N, 11.63, Found: C, 69.95; H, 5.20; N, 11.66%.

- 2-[(4-nitrophenyl)methylenehydrazino]-7-methoxy-4,5-dihydroanthaleno[d] thiazole (XIIe): Yield (78%), mp 220-222°C; IR (KBr) δ max/(v. cm⁻¹): 3457 (NH), 3078 (CH=Ar), 2927 (CH-sp), 1628 (C=N), 1557 (NO₂, asymmetric), 1336 (NO₂, symmetric) and 1247 (C-O); ¹H NMR (DMSO-d₆, δ ppm): 2.81 (t, 2H, CH₂), 7.23-8.25 (m, 7H, Ar-H), 9.46 (s, 1H, NH, D₂O exchangeable); Anal. Calcd. For C₂₁H₁₃N₂O₄S (380.45): C, 59.98; H, 4.24; N, 14.73, Found: C, 59.72; H, 4.04; N, 14.92%.

Antimicrobial evaluation

Materials

All microorganisms used were obtained from the culture collection of the Department of Microbiology and Immunology, Faculty of Pharmacy, Helwan University. The compounds were tested against E. coli and S. aureus in broths at pH 7 and against B. subtilis in bacto brain heart infusion broth at pH 7 and against C. albicans in broth containing 1% neopeptone and 2% dextrose at pH 5.7 Media for disc sensitivity tests were nutrient agar and Muller Hinton agar (MHA) purchased from Difco. The disc diameter was 6 mm. Non sterile powder of the tested compounds were dissolved in sterile DMSO to yield 5 mg/ ml passed through 0.2 μm membrane filters (Millipore corp. Bedford, Mass).

Methods

Disc diffusion test

20 mL of Muller-Hinton agar (MHA) at 55°C, inoculated with 1 mL of the microbial culture (10⁶ CFU/Ml), was poured in sterile Petri dish and left to solidify. A sterile filter paper disk impregnated with solution of the compound under testing (100 μg/mL in DMF) was placed on the surface of agar, and the plate was incubated overnight at 37°C. The diameter of the zone of inhibition was measured and compared with the standard zone produced by amoxicillin.

Tube dilution technique

Nine dilutions of the tested compounds were made in Mueller-Hinton broth to obtain test concentrations ranging from 50 to 0.2 μg/mL. The concentrations of the microorganism were adjusted as to give an inoculum of 10⁶ CFU in each tube. The tubes were incubated overnight at 37°C. The inhibitory concentration was determined and compared to that of Amphotericin B, Clotrimazole and Ketoconazole.

RESULTS AND DISCUSSION

Chemistry

The starting material 6-methoxy-1-tetralone I, comprises a cyclic butenerphenone which is suitable to furnish the versatile intermediate β-unsaturated ketones, the chalcones IIa-f. These chalcones were synthesized via Claisen-Schmidt condensation, a type of aldol condensation of aromatic aldehydes with the corresponding substituted acetophenone in the presence of sodium, potassium or barium hydroxide [39,40] as illustrated in Scheme 1.

The reaction of 1 with different aromatic aldehydes namely, p-chlorobenzaldehyde, p-dimethylaminobenzaldehyde, 3,4-dimethoxybenzaldehyde, nitrilalanaldehyde, p-nitrobenzaldehyde and m-methoxy-benzaldehyde, in the presence of 10% potassium hydroxide uneventfully afforded the corresponding 2-[(substituted phenyl)methylene]-6-methoxy-3,4-dihydro1(2H)-naphthalenones IIa-f in 65-90% yields. The structures of compounds IIa-f were confirmed by microanalytical analyses and spectral data (IR, ¹H-NMR and mass spectra). The IR spectra showed the characteristic carbonyl stretching bands at 1637-1663 cm⁻¹ in addition to other bands correlating with their structures. The ¹H-NMR spectrum of IIa, as an example, revealed two triplets at δ 2.91, 3.14 ppm referring to the C₃ and C₄ alicyclic methylene protons, two singlet signals at δ 3.93, 6.71 ppm attributed to OCH₃, and the vinyl proton respectively, alongside multiplet signals at δ 6.80-8.22 ppm attributed to the seven aromatic protons of the compound. The mass spectrum of the same compound showed two isotopic molecular ion peaks at m/z 297 and 299 which is in agreement with its molecular formula. In addition, the mass spectra of the chalcone derivatives.
IIb-f exhibited the molecular ion peaks of the compounds confirming their structural formula.

These chalcones are considered to be useful intermediates in several cyclization reactions to produce different types of heterocyclic compounds according to the used reactants and the reaction's conditions[30,41]. Thus, in the present investigation, the target quinazolines IIIa,b, VIa,b and Va,b were obtained by condensation of the prepared chalcones IIa,b with urea, thiourea and guanidine salt respectively in refluxing ethanol under alkaline medium conditions. The appearance of the absorption bands of the NH and C=O groups at 3444 and 1668 cm⁻¹, respectively in the IR spectrum of compound IIb agreed with the proposed structure. In addition, the 1H-NMR spectrum of compound IIIa revealed the disappearance of the vinylic proton singlet assigned for IIa, and the presence of the alicyclic and methoxy protons at δ 2.91, 3.14 and 3.93 ppm respectively in addition to multiplet signals at δ 6.90-7.96 ppm for the seven aromatic protons.

Furthermore, the mass spectra of IIIa and IIb displayed the molecular ion peaks which were in agreement with the proposed structures in addition to a common peak at m/z 229 assigned to a molecular fragment ion with side chain p-substituted phenyl missing moiety.

The quinoline analogs VI, VII and VIII could have been synthesized as cited in the literature through a base catalyzed cyclocondensation reaction of α,β-unsaturated ketones with ethylcyanoacetate in the presence of ammonium acetate [42]. This method is time consuming and suffers from some difficulties especially with propenones bearing heterocyclic moieties. Another approach involves the condensation of an active acetyl function and the appropriate arylidinocyanoacetate, arylidinithiocyanatoacetamide or arylidinemononitrile in the presence of ammonium acetate as a source of ammonia [43]. The one-step multi-component reaction approach was effectively employed since it is easy to perform and gives better yields in less reaction times.

The IR spectra for compounds VIa-g showed stretching bands at 3462-3281, 2212-2219 and 1635-1715 cm⁻¹ corresponding to NH, CN and C=O groups, respectively. The 1H-NMR spectrum of compound VIa displayed a broad D₂O exchangeable singlet signal at δ12.5 ppm attributed to the lactam proton, alongside multiple signals at δ 6.9-8.1 ppm for the seven aromatic protons. The MS spectrum of compound VIIIa displayed a base peak at m/z 361 attributed for its molecular ion.

<table>
<thead>
<tr>
<th>Compound</th>
<th>B. subtilis</th>
<th>S. aureus</th>
<th>E. Coli</th>
<th>C. albicans</th>
</tr>
</thead>
<tbody>
<tr>
<td>IX</td>
<td>18&quot;**</td>
<td>11&quot;</td>
<td>--</td>
<td>16&quot;**</td>
</tr>
<tr>
<td>X</td>
<td>16&quot;**</td>
<td>14&quot;</td>
<td>16&quot;**</td>
<td>19&quot;**</td>
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<tr>
<td>XIa</td>
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<tr>
<td>XIb</td>
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<td>--</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>10</td>
<td>--</td>
<td>8</td>
<td>--</td>
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</tbody>
</table>

The sensitivity of the microorganisms towards the tested compounds is identified in the following manner: * significant. ** Highly significant.

Bromination of the starting derivative I in glacial acetic acid yielded the corresponding 2-bromo-6-methoxy-1-tetralone IX. Synthesis of the desired aminothiazole derivative X in 80% yield was achieved by allowing IX to react with thiourea in boiling ethanol. The IR spectrum of the latter compound showed the absence of C=O band at 1670 cm⁻¹ and the presence of bands of NH and C=N at 3254, 3204 and 1623 cm⁻¹. While 1H-NMR spectrum of the same compound exhibited a singlet signal due to NH proton (D₂O exchangeable) at δ 9.14 ppm, in addition to the expected two alicyclic methylenes, methoxy and aromatic protons at δ 2.72, 2.90, 3.91 and 6.93-8.15 ppm, respectively. Moreover, the MS spectrum of compound X confirmed the proposed structure as it showed a molecular ion peak, which is also the base peak at m/z 232. Similarly, condensation of the α-bromoketone IX with the appropriate aromatic aldehydethiosemicarbazones namely 4-chlorobenzaldehyde- thiosemicarbazone, 4-dimethylaminobenzaldehydethiosemicarbazone, 1,3,4-dimethoxy- benzaldehydethiosemicarbazone, cinnamaldehydethiosemicarbazone, and 4-nitrobenzaldehydethiosemicarbazone was carried out in refluxing DMF for 4-6 hours to precipitate the desired 4,5-dihydronaphtho[1,2-d]thiazolo compounds XI in 65-80% yield. The absence of C=O band and the presence of NH and C=N bands at 3402-3204 and 1623-1628 cm⁻¹, respectively in the IR spectra of the prepared compounds confirmed their structures. 1H-NMR spectrum of XIe showed the azomethine proton of N=CH moiety at δ 6.82 ppm and the seven aromatic protons at the region δ 7.21-8.20 ppm. In addition, the MS spectrum of compound XIa confirmed its proposed structure as it showed the molecular ion peak at m/z 369 of 56%.

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relative abundance, while the base peak of the most stable fragment was at 229 m/z.

Antimicrobial evaluation

Antimicrobial screening

Eighteen out of the newly synthesized compounds were selected as representative examples to evaluate their antibacterial and antifungal activities. The tested compounds were screened in vitro against two pathogenic gram-positive bacteria viz. Staphylococcus aureus ATCC 29213 and B. Subtilis ATCC6633, the pathogenic gram-negative bacteria E. coli ATCC 2592and fungal culture Candida Albicans NRRL Y-477. The tests were carried out with the target compounds and the reference drugs, under identical conditions by the agar well diffusion method using 100 μL of suspension containing 1 x 10⁸ CFU/mL of the pathological tested bacteria and 1 x 10⁸ CFU/mL of yeast spread on nutrient agar (NA), and Sabour and dextrose agar (SDA) respectively. The obtained data were recorded for each tested compound as the average diameter of inhibition zones (IZ) of bacterial or fungal growth around the discs in mm. The reference drugs were amoxicillin for antibacterial and amphotricin B, clotrimazole and ketoconazole for antifungal tests, respectively.

Furthermore, the minimum inhibitory concentration (MIC) measurement (expressed in μg/mL) was determined for the most active compound X that showed significant growth inhibition zones using the two-fold serial dilution method. The diameter of inhibition zones of the screened compounds are recorded in table (1).

According to table (1), it could be investigated that the polycyclic 2-aminothiazole derivative X showed significant broad spectrum antimicrobial activity against all of the tested organisms while the 2-bromo derivative IX showed remarkable activity against only the pathogenic Staphylococcus aureus ATCC 29213 gram (+) bacteria and the selected fungal strain Candida Albicans but inactive against the selected gram (-) bacteria. Based on the MIC values, the derivative X exhibited poor antifungal activity (MIC = 1.85 mg/mL) compared to amphotricin B (4-0.05 μg/mL), clotrimazole (50-0.01 μg/mL) and ketoconazole (100-0.01 μg/mL).

CONCLUSION

New series of tricyclic benzo[h]quinazolines, benzo[h]quinolines and naphthalene[d]thiazoles derivatives were designed as bioisosteres and synthesized using 6-methoxy-1-tetralone as a key starting material. The new compounds were evaluated as antibacterial and antifungal agents. The 2-aminothiazole derivative X investigated significant broad spectrum antimicrobial activity against all of the tested pathogenic organisms comparing to the reference drugs amoxicillin, amphotricin B, clotrimazole and ketoconazole, while the 2-bromo derivative IX showed excellent potency against the tested gram (+) bacterial and fungal strains, but its activity was abolished against the tested gram (-) bacterial strain.

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Conflict of Interest

The authors declare that they do not have any conflict of interest.

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