ISSN: 2357-0547 (Print)
ISSN: 2357-0539 (Online)

Research Article / JAPR
Ebied et al., 2017, 1 (4), 216-227

Journal of Advanced Pharmacy Research

Synthesis and Antimicrobial Evaluation of Some Tricyclic Substituted Benzo[*h*]quinazolines, Benzo[*h*]quinolines and Naphthaleno[*d*]thiazoles

Mohammed Y. Ebied[1], Wafaa A. Zaghary[2], Kamelia M. Amin[1], Sherif F. Hammad [2]*

[1]*Pharmaceutical Chemistry Department, Faculty of Pharmacy, Cairo University, Cairo, Egypt.*
[2]*Pharmaceutical 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: +20225541601*
E-mail address: sherifhammad2010@hotmail.com

Submitted on: 25-07-2017; Revised on: 14-09-2017; Accepted on: 24-09-2017

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 & XIa-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 thiocyanoacetamide in the presence of excess ammonium acetate afforded benzo[*h*]quinolines compounds **VIa-g**, **VIIa-c** and **VIIIa-c** respectively. Naphthaleno[*d*]thiazoles **X & XIa-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** was1.85 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 treatment[1,2].

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 medications[3]. Quinazoline nucleus is one of fused heterocyclic ring systems that possesses a wide array of biological activities. These pharmacological activities include DNA binding[4], antitumor[5-7], benzodiazepine and GABA receptor ligand activity[8], antiviral[9,10], antibacterial[11], anti-tuberculosis[12,13] and cellular phosphorylation and tyrosine kinase inhibition[14]. Many marketed drugs comprise quinazoline nucleus in their structures such as;

the α_1-blocker alfuzocin, which is used in the treatment of BPH (benign prostate hyperplasia), the oral hypoglycemic balaglitazone, dacomitinibthat is used in the treatment of non-small-cell lung carcinoma (in phase III clinical trials) and the broad-spectrum antifungal albaconazole[15] (**Figure 1**).

Similarly, quinoline condensed ring system has been found in a considerable number of pharmacologically active natural products and in clinically active drugs[16-18]. The broad diversity of pharmacological activities of quinoline-containing compounds includes antipsychotic[19], anti-inflammatory [20,21], antioxidant [22], anti-HIV[23], antifungal[24], treatment of lupus[25], treatment of neurodegenerative diseases[26], anti-tubercular [27,28], antiprotozoal [29,30] and anticancer[31,32]. 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 tipifarnibusedfor the treatment of leukemia [33] (**Figure 2**).

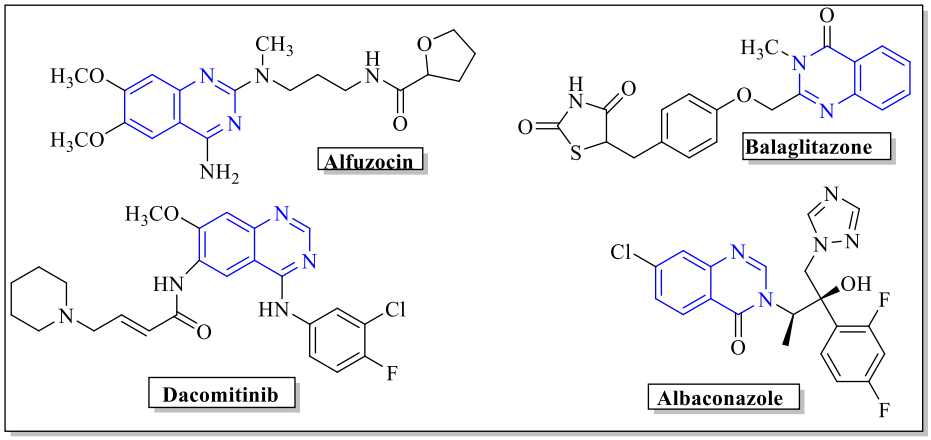


Figure. 1. Representative examples of marketed and clinically active quinazoline-containing Drugs

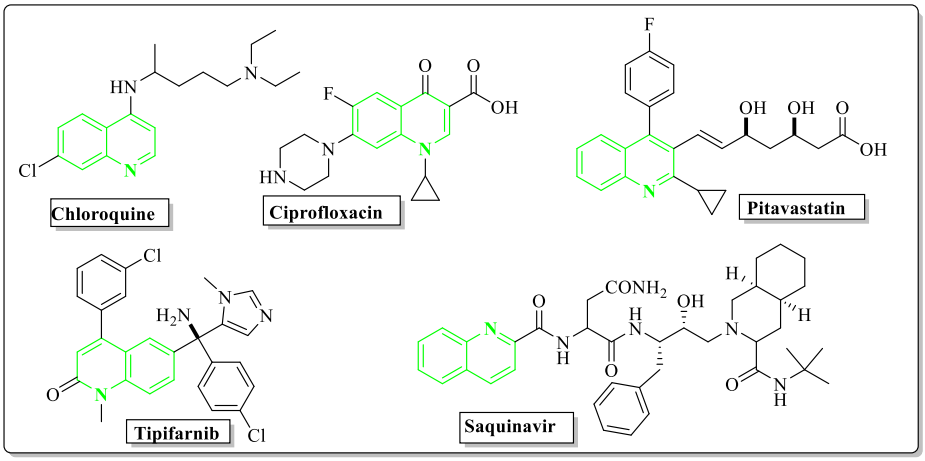


Figure. 2. Representative examples of marketed quinoline-containing Drugs

Moreover, benzothiazole fused heterocyclic scaffold has been reported to have a relatively variable pharmacological effects such as antimicrobial[34], anticancer[35,36], anti-inflammatory [37], β-2 adrenoceptor agonist and antidepressant activities[38]. **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 T[38].

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

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_2SO_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 MH 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.

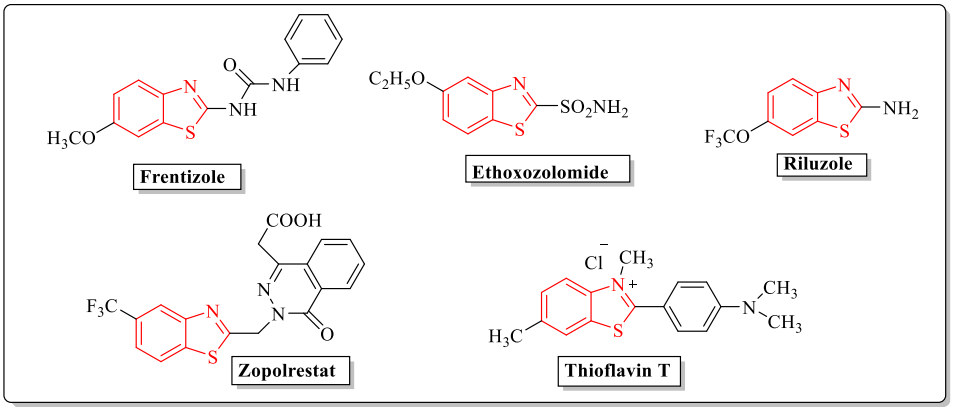
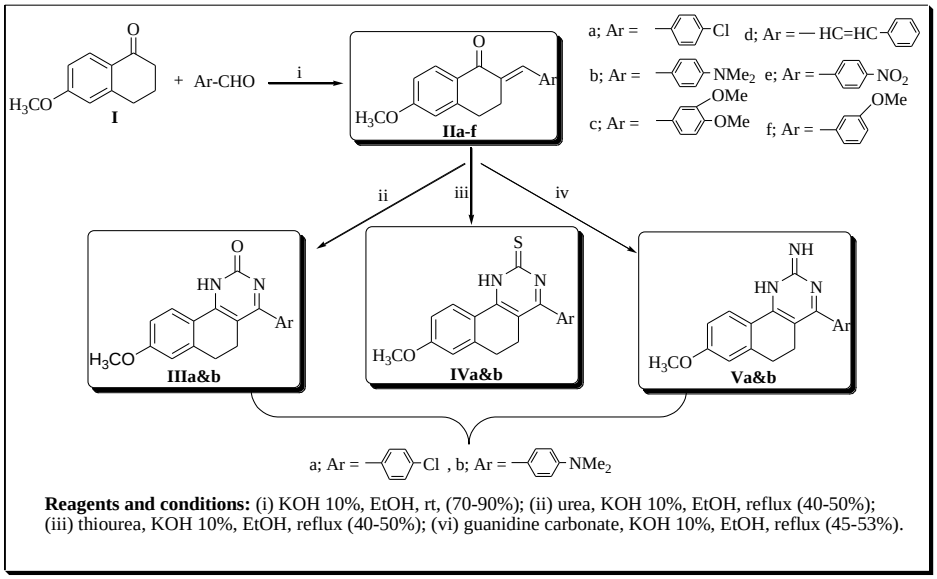
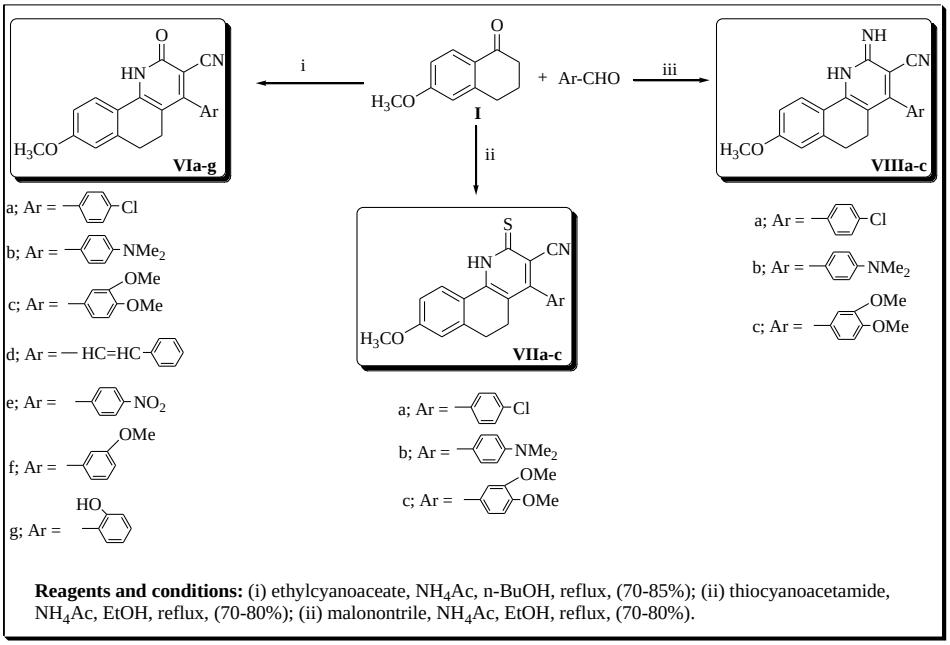


Figure. 3. Representative examples of marketed benzothiazole-containing Drugs



Scheme 1. Synthesis of *α,β*-unsaturated ketones **IIa-f**, quinazolinones **IIIa &b,** quinazolinethiones **VIa&b** and iminioquinazolines **Va&b**



Scheme 2. Synthesis of benzo[*h*]quinoline derivatives **VIa-g**, **VIIa-d** and **VIIIa-c**.

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,cinnamaldehyde, 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)-naphthalenone (IIa):** Yield (85%), mp 158-160 °C; IR (KBr) δ max/(ν. cm^{-1}): 3055 (CH-Ar), 2950, 2925 (CH-sp3), 1660 (C=O) and (1274, C-O); ^{1}H NMR ($CDCl_3$, δ ppm): 2.91, (t, 2H, CH_2), 3.14 (t, 2H, CH_2), 3.93 (s, 3H, OCH_3), 6.71 (s, 1H, =CH-), 6.80-8.22 (m, 7H, Ar-H); MS m/z (R.A.%): $M^{+\cdot}$ 297 (100), $[M+2]^{+\cdot}$ 299 (43), 270 (18.8); Anal.Calcd. For $C_{18}H_{15}ClO_2$ (298.77): C, 72.36; H, 5.06, Found: C, 72.69; H, 5.06%.
- **2-[(*p*-Dimethylaminophenyl)methylene]-6-methoxy-3,4-dihydro-1(2*H*)-naph- thalenone (IIb):** Yield (70%), mp 43-45 °C; IR (KBr) δ max/(ν. cm^{-1})**:** 3067 (CH-Ar), 2942, 2927 (CH-sp3), 1637 (C=O) and (1245, C-O); MS m/z (R.A.%); $M^{+\cdot}$ 308 (100); Anal. Calcd. For $C_{20}H_{21}NO_2$ (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(2*H*)-naphthalenone** (**IIc**)**:**Yield (75%), mp 98-100 °C; IR (KBr) δ max/(ν. cm^{-1}): 3088 (CH-Ar), 2961, 2927 (CH-sp3), 1654 (C=O) and (1250, C-O); Anal. Calcd. For $C_{20}H_{20}O_4$ (324.37): C, 74.06; H, 6.22, Found: C, 74.23; H, 6.30%.
- **2-[Cinnamomethylene]-6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (IId):**Yield (85%), mp 138-140 °C; MS m/z (R.A.%); $M^{+\cdot}$ 290 (100); Anal. Calcd. For $C_{20}H_{18}O_2$ (290.36): C, 82.73; H, 6.25; Found: C, 83.1 0; H, 6.31%.
- **2-[(*p*-Nitrophenyl)methylene]-6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (IIe):**Yield (90%), mp 168-170 °C; IR (KBr) δ max/(ν. cm^{-1}): 3092 (CH-Ar), 2934 (CH-sp3), 1663 (C=O), 1514 (NO_2, asymmetric), 1342 (NO_2, symmetric) and (1270, C-O); MS m/z (R.A.%): $M^{+\cdot}$ 308 (100); Anal. Calcd. For $C_{18}H_{15}NO_4$ (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(2*H*)- naphthalene one (IIf):**Yield (80%), mp 78-80 °C; IR (KBr) δ max/(ν. cm-1); 3055 (CH-Ar), 2950, 2925 (CH-sp3), 1659 (C=O) and (1255, C-O); ^{1}H NMR ($CDCl_3$, δ ppm): 2.91 (t, 2H, CH_2) , 3.14 (t, 2H, CH_2), 3.86 (s,3H, OCH_3), 3.95 (s,3H, OCH_3), 6.71 (s, 1H, =CH-), 6.89-8.25 (m, 7H, Ar-H); Anal.Calcd. For $C_{19}H_{18}O3$ (294.35): C, 77.53; H, 6.16, Found: C, 77.63; H, 6.25.

General procedure for the synthesis of quinazolinesIIIa&b, IVa&b and Va&b

An alcoholic solution of urea, thiourea or guanidine carbonate (0.01mol) in absolute ethanol (10 mL) was added to a mixture of the appropriate chalcones **IIa** and/or **IIb** (0.01mol), potassium hydroxide (1.12g, 0.02 mol) in absolute ethanol (30 mL). The reaction

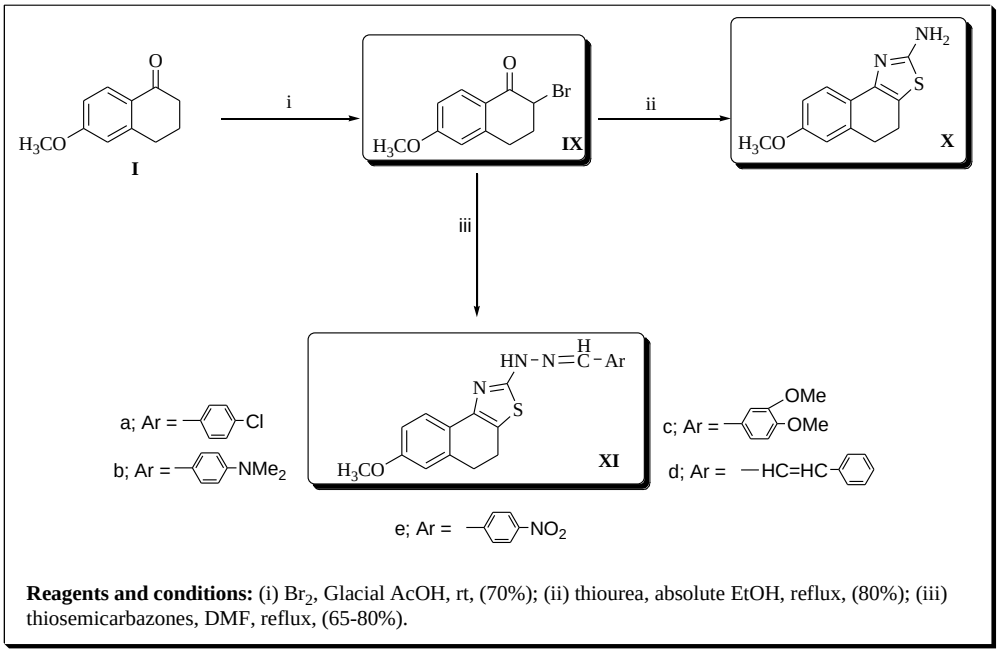
mixture was allowed to reflux for 6 h and the solvent was removed under reduced pressure. The separated residue was washed with water and crystallized from ethanol.

- **4-(4-Chlorophenyl)-8-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[*h*]quinazoline (IIIa):** Yield (40%), mp 158-160 °C; IR (KBr) δ max/(ν. cm^{-1})**:** 3340 (NH), 3050 (CH-Ar), 2944 (CH-sp3), 1659 (C=O) and (1273, C-O); ^{1}H NMR (DMSO-*d6*, δ 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_2O exchangeable); MS m/z (R.A.%): $M^{+\cdot}$ 339 (28), $[M+2]^{+\cdot}$ 341 (9); Anal.Calcd. For $C_{19}H_{15}ClN_2O_2$ (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-tetrahydro-benzo[*h*]quinazoline (IIIb):** Yield (50%), mp 167-170 °C; IR (KBr) δ max/(ν. cm^{-1}); 3344 (NH), 3192 (CH-Ar), 2937 (CH-aliphatic), 1668 (C=O) and (1274, C-O); MS m/z (R.A.%); $M^{+\cdot}$ 348 (100); Anal. Calcd. For $C_{21}H_{21}N_3O_2$ (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*]quinazo- line (IVa):Yield (50%), mp 238-240 °C; IR(KBr) δ max/(ν. cm^{-1}); 3271 (NH), 3108 (CH-Ar), 2926 (CH-sp3), 1295 (C=S) and (1248, C-O); ^{1}H NMR ($CDCl_3$, δ 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_2O exchangeable); MS m/z (R.A.%): $M^{+\cdot}$ 339 (28), $[M+2]^{+\cdot}$ 341 (10); Anal.Calcd. For $C_{19}H_{15}ClN_2OS$ (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 (40%), mp 220-222 °C; IR(KBr) δ max/(ν. cm^{-1}): 3270 (NH), 3100 (CH-Ar), 2920 (CH-sp3), 1294 (C=S) and (1248, C-O); MS m/z (R.A.%); $M^{+\cdot}$363 (44); Anal. Calcd. For $C_{21}H_{21}N_3OS$ (363.48): C, 69.39; H, 5.82; N, 11.56, Found: C, 69.32; H, 5.35; N, 11.53%.
- **4-(4-Chlorophenyl)-8-methoxy-2-imino-1,2,5,6-tetrahydrobenzo[h]quinazolines (Va)**:Yield (53%), mp 162-164 °C; IR(KBr) δ max/(ν. cm^{-1}): 3346 (NH), 3188 (CH-Ar), 2951 (CH-sp3), 1604 (C=N) and (1249, C-O); MS m/z (R.A.%): $M^{+\cdot}$ 337 (100), $[M+2]^{+\cdot}$ 339 (34); Anal. Calcd. For $C_{19}H_{16}ClN_3O$ (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*]quinazoline (Vb): Yield (45%), mp 260-262 °C; IR(KBr) δ max/(ν. cm^{-1}); 3271 (NH), 2999 (CH-Ar), 2940 (CH-sp3), 1607 (C=N) and (1245, C-O);^{1}H NMR ($CDCl_3$, δ 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_2O exchangeable); MS m/z (R.A.%): $M^{+\cdot}$ 345 (98.8); Anal.Calcd. For $C_{21}H_{22}N_4O$ (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_2O exchangeable); MS m/z (R.A.%): $M^{+\cdot}$ 339 (28), $[M+2]^{+\cdot}$ 341 (10); Anal.Calcd. For $C_{19}H_{15}ClN_2OS$ (354.87): C, 64.30; H, 4.26; N, 7.89, Found: C, 63.88; H, 4.35; N, 7.50%.



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

- **4-(4-Dimethylaminophenyl)-8-methoxy-2-thioxo-1,2,5,6-tetrahydrobenzo[*h*]quinazoline (IVb):** Yield (40%), mp 220-222°C; IR(KBr) δ max/(ν. cm^{-1}): 3270 (NH), 3100 (CH-Ar), 2920 (CH-sp3), 1294 (C=S) and (1248, C-O); MS m/z (R.A.%); $M^{+\cdot}$363 (44); Anal. Calcd. For $C_{21}H_{21}N_3OS$ (363.48): C, 69.39; H, 5.82; N, 11.56, Found: C, 69.32; H, 5.35; N, 11.53%.
- **4-(4-Chlorophenyl)-8-methoxy-2-imino-1,2,5,6-tetrahydrobenzo[h]quinazolines (Va)**:Yield (53%), mp 162-164°C; IR(KBr) δ max/(ν. cm^{-1}): 3346 (NH), 3188 (CH-Ar), 2951 (CH-sp3), 1604 (C=N) and (1249, C-O); MS m/z (R.A.%): $M^{+\cdot}$ 337 (100), $[M+2]^{+\cdot}$ 339 (34); Anal. Calcd. For $C_{19}H_{16}ClN_3O$ (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*]quinazoline (Vb):** Yield (45%), mp 260-262 °C; IR(KBr) δ max/(ν. cm^{-1}); 3271 (NH), 2999 (CH-Ar), 2940 (CH-sp3), 1607 (C=N) and (1245, C-O);^{1}H NMR ($CDCl_3$, δ 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_2O exchangeable); MS m/z (R.A.%): $M^{+\cdot}$ 345 (98.8); Anal.Calcd. For $C_{21}H_{22}N_4O$ (346.43): C, 72.81; H, 6.40; N, 16.17, Found: C, 72.80; H, 6.20; N, 16.16%.

General procedure for the synthesis of quinolines VIa-g

A mixture of 6-methoxy-1-tetralone **I** (1.78 g, 0.01mol), ethylcyanoacetate (1.2 g, 0.01mol), the appropriate aromatic aldehydes namely; p-chlorobenzaldehyde, 4-Dimethyl- benzaldehyde,3,4-dimethoxybenzaldehyde,cinnamaldehyde, p-nitrobenz-aldehyde, 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-canbonitrile** (**VIa**):Yield (78%), mp 260-262°C; IR (KBr) δ max/(ν. cm^{-1}); 3420 (NH), 3082 (CH-Ar), 2930 (CH-sp3), 2219 (CN), 1635 (C=O) and (1257, C-O); ^{1}H NMR (DMSO-d_6, δ ppm):2.42 (t, 2H, CH_2) , 2.81 (t, 2H, CH_2) , 3.91 (s, 3H, OCH_3), 7.03-8.15 (m, 7H, Ar-H), 9.46 (s, 1H, NH, D_2O exchangeable); MS m/z (R.A.%): $M^{+\cdot}$ 362 (100), $[M+2]^{+\cdot}$ 364 (38); Anal.Calcd. For $C_{21}H_{15}ClN_2O_2$ (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*]qui- nolone-3-cabonitrile** (**VIb**):Yield (74%), mp 260-262°C; IR (KBr) δ max/(ν. cm^{-1}): 3450 (NH), 3125 (CH-Ar), 2913 (CH-sp3), 2212 (CN), 1670 (C=O) and (1257, C-O); Anal. Calcd. For $C_{23}H_{21}N_3O_2$ (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]quino- lone-3-carbonitrile** (**VIc**):Yield (80%), mp>300°C; IR (KBr) δ max/(ν. cm^{-1}): 3284 (NH), 3075 (CH-Ar), 2940 (CH-sp3), 2224 (CN), 1715 (C=O) and (1251, C-O); MS m/z (R.A.%); $M^{+\cdot}$ 388 (100); Anal. Calcd. For $C_{23}H_{20}N_2O_4$ (388.42): C, 71.12; H, 5.19; N, 7.2 1, Found: C, 71.58; H, 5.14; N, 7.25%.
- **4-(Cinnamyl)-8-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[*h*]quinoline-3-carbonintrile (VId):** Yield (75%), mp 290-292°C; IR (KBr) δ max/(ν. cm^{-1}); 3281 (NH), 3079 (CH-Ar), 2933 (CH-sp3), 2219 (CN), 1629 (C=O) and (1253, C-O);^{1}H NMR ($CDCl_3$, δ ppm):2.72 (t, 2H, CH_2) , 2.93 (t, 2H, CH_2), 3.95 (s,3H, OCH_3), 7.01 (d, 1H, -CH=), 7.12 (d, 1H, -CH=), 7.31-8.24 (m, 8H, Ar-H), 9.41 (s, 1H, NH, D_2O exchangeable); Anal.Calcd. For $C_{23}H_{18}N_2O_2$ (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-canbonitrile (VIe):** Yield (82%), mp 240-242°C; IR (KBr) δ max/(ν. cm^{-1}): 3419 (NH), 3135 (CH-Ar), 2924 (CH-sp3), 2217 (CN), 1640 (C=O), 1535 (NO_2, asymmetric), 1349 (NO_2 sym.) and (1250, C-O); Anal. Calcd. For $C_{21}H_{15}N_3O_4$ (373.37): C, 67.55; H, 4.05; N, 11.26, Found: C, 67.62; H, 4.27; N, 11.76%.
- **4-(3-Methoxyphenyl)-8-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[*h*]quinolo- ne-3-carbonitrile** (**VIf**): Yield (85%), mp 278-280°C; IR (KBr) δ max/(ν. cm^{-1}); 3287 (NH), 3085 (CH-Ar), 2950 (CH-sp3), 2219 (CN), 1705 (C=O) and (1250, C-O); MS m/z (R.A.%): $M^{+\cdot}$ 358 (100);Anal. Calcd. For $C_{22}H_{18}N_2O_3$ (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*]quinol-one-3-carbonitrile** (**VIg**):Yield (70%), mp 258-260°C; IR (KBr) δ max/(ν. cm^{-1}); 3482 (OH), 3288 (NH), 3095 (CH-Ar), 2940 (CH-sp3), 2218 (CN), 1705 (C=O) and (1259, C-O); Anal. Calcd. For $C_{21}H_{16}N_2O_3$ (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 **I** (1.78g, 0.01 mol), the appropriate aromatic aldehydes namely; *p*-chlorobenzaldehyde, *p*-dimethylaminobenzaldehyde and 3,4-dimethoxybenzaldehyde (0.01 mol), of thiocyanoacetamide (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*]quinol- ine-3-canbonitrile (VIIa)**:Yield (72%), mp 105-107 °C; IR (KBr) δ max/(ν. cm^{-1}): 3360 (NH), 3142 (CH-Ar), 2942 (CH-sp3), 2209 (CN), 1347 (C=S) and (1251, C-O); MS m/z (R.A.%): $M^{+\cdot}$ 377 (10), $[M+2]^{+\cdot}$ 379 (3); Anal. Calcd. For $C_{21}H_{15}ClN_2OS$ (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-cabonitrile(VIIb)**:Yield (70%), mp 208-210 ° C; IR (KBr) δ max/(ν. cm^{-1}); 3388 (NH), 3060 (CH-Ar), 2929 (CH-sp3), 2208 (CN), 1371 (C=S) and (1256, C-O); Anal. Calcd. For $C_{23}H_{21}N_3OS$ (387.50): C, 71.29; H, 5.46; N, 10.84, Found: C, 71.27; H, 5.05; N, 10.38%.
- **4-(3,4-Dimethoxyphenyl)-8-methoxy-2-thioxo-1,2,5,6-tetrahy drobenzo[*h*]qui-nolone-3-carbonitrile (VIIc)**: Yield (75%), mp 268-270 °C; IR (KBr) δ max/(ν. cm^{-1}); 3448 (NH), 3060 (CH-Ar), 2935 (CH-sp3), 2215 (CN), 1373 (C=S) and (1258, C-O);^{1}H NMR ($CDCl_3$, δ ppm): 2.81 (s, 4H, $(CH_2)_2$) 3.86 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 6.71-8.13 (m, 6H, Ar-H), 9.41 (s, 1H, NH, D_2O exchangeable); Anal.Calcd. For $C_{23}H_{20}N_2O_3S$ (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-dimethoxybenzladehyde (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*]quino- line-3-canbonitrile (VIIIa)**: Yield (65%), mp 203-205 ° C; IR (KBr) δ max/(ν. 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.%): $M^{+\cdot}$ 361 (100), $[M+2]^{+\cdot}$363 (37); Anal. Calcd. For $C_{21}H_{16}Cl\ N_3O$ (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*]quinolone-3-cabonitrile (VIIIb)**:Yield (70%), mp 178-180 ° C; IR (KBr) δ max/(ν. cm-1): 3459 (NH, asymmetric), 3357 (NH, sym), 3088 (CH-Ar), 2938 (CH-sp3), 2212 (CN), and 1248 (C-O); ^{1}H NMR ($CDCl_3$, δ ppm): 2.82 (s, 4H, $(CH_2)_2$, 3.11 (s, 6H, $N(CH_3)_2$), 3.93 (s, 3H, OCH_3), 6.72-8.11 (m, 7H, Ar-H), 9.46, 9.61 (2s, 2H, 2NH, D_2O exchangeable);MS m/z (R.A.%): $M^{+\cdot}$ 370 (100); Anal. Calcd. For $C_{23}H_{22}N_4O$ (370.46): C, 74.57; H, 5.99; N, 15.13, Found: C, 74.50; H, 6.30; N, 15.42%.
- **4-(3,4-Dimethoxyphenyl)-8-methoxy-2-imino-1,2,5,6-tetrahydrobenzo[*h*]quinolone-3-carbonitrile (VIIIc):** Yield (68%), mp 170-172 ° C; IR (KBr) δ max/(ν. cm^{-1}): 3475 (NH, asymmetric), 3361 (NH, sym), 3085 (CH-Ar), 2944 (CH-sp3), 2203 (CN), and 1263 (C-O); Anal. Calcd. For $C_{23}H_{21}N_3O_3$ (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/(ν. cm-1): 3058 (CH-Ar), 2934 (CH-sp3), 1672 (C=O), and 1263 (C-O); MS m/z (R.A.%): $M^{+\cdot}$254 (14.44), $[M+2]^{+\cdot}$256 (14.88); Anal. Calcd. For $C_{11}H_{11}BrO_2$ (255.11): C, 51.79; H, 4.35, Found: C, 51.56; H, 4.63%.
- **7-Methoxy-4,5-dihydronaphtho[1,2-d]thiazolyl-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/(ν. cm^{-1}): 3254 (NH), 3064 (CH-Ar), 2972 (CH-sp3), 1633 (C=N), and 1248 (C-O); ^{1}H NMR (DMSO-d_6, δ ppm): 2.72 (t, 2H, CH_2) , 2.91 (t, 2H, CH_2), 3.9 (s, 3H, OCH_3), 4.56 (s, 2H, NH_2, D_2O exchangeable), 6.91-8.12 (m, 3H , Ar-H); MS m/z (R.A.%); $M^{+\cdot}$ 232 (100); Anal. Calcd. For $C_{12}H_{12}N_2OS$ (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-dihydronaphtho [1,2-*d*]thiazol-2-yl)hydrazines (XIa-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 benzaldehydethiosemcarbazone,cinnamaldehydethiose micarbazone and *p*-nitrobenzaldehthiosemicarbzone (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 **XIa-e**.

- **2-(4-Chorophenyl)methylenehydrazino]-7-methoxy-4,5-dihydronaphthaleno[*d*]thiazole (XIa)**:Yield (75%), mp 170-172 °C; IR (KBr) δ max/(ν. cm^{-1}): 3421 (NH), 3060 (CH-Ar), 2925 (CH-sp3), 1623 (C=N), and 1247 (C-O); MS m/z (R.A.%): $M^{+\cdot}$ 369 (14.44), 229 (100); Anal. Calcd. For $C_{19}H_{16}ClN_3OS$

(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-dihydronaphthaleno [*d*]thiazole** (**XIb**): Yield (80%), mp 116-118 ° C; IR (KBr) δ max/(ν. cm^{-1}): 3378 (NH), 3060 (CH-Ar), 2891 (CH-sp3), 1605 (C=N) and 1248 (C-O); Anal. Calcd. For $C_{21}H_{22}N_4OS$ (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-dihydronaph- thaleno[*d*] thiazole** (**XIc**):Yield (65%), mp 204-206 ° C; IR (KBr) δ max/(ν. cm^{-1}): 3402 (NH), 3073 (CH-Ar), 2936 (CH-sp3), 1624 (C=N) and 1256 (C-O); Anal. Calcd. For $C_{21}H_{21}N_3O_3S$ (395.48): 63.78; H, 5.35; N, 10.63, Found: C, 63.17; H, 5.59; N, 10.86%.
- **2-[(Cinnamyl)methylenehydrazino]-7-methoxy-4,5-dihydronaphthaleno[*d*]thiazole**(**XId**); Yield (74%), mp 180-182 ° C; IR (KBr) δ max/(ν. cm^{-1}): 3381 (NH), 3045 (CH-Ar), 2931 (CH-sp3), 1610 (C=N) and 1247 (C-O); ^{1}H NMR ($CDCl_3$, δ ppm): 2.91 (t, 2H, CH_2), 3.11 (t, 2H, CH_2), 3.95 (s, 3H, OCH_3), 6.83–7.13 (m, 3H, -CH=), 7.22-8.24 (m, 8H, Ar-H), 9.40, (s, 1H, NH, D_2O exchangeable); Anal.Calcd. For $C_{21}H_{19}N_3OS$ (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-dihydronaphthaleno-[*d*]thiazole** (**XIe**):Yield (78%), mp 220-222 ° C; IR (KBr) δ max/(ν. cm^{-1}): 3457 (NH), 3078 (CH-Ar), 2927 (CH-sp3), 1628 (C=N), 1557 (NO_2, asymmetric), 1336 (NO_2, symmetric) and 1247 (C-O); ^{1}H NMR (DMSO-d_6, δ ppm): 2.81 (t, 2H, CH_2), 2.92 (t, 2H, CH_2), 3.95 (s, 3H, OCH_3), 6.83 (s, 1H, -CH=), 7.23-8.25 (m, 7H, Ar-H), 9.46 (s, 1H, NH, D_2O exchangeable); Anal.Calcd. For $C_{19}H_{16}N_3O_3S$ (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*innutient broth 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 mLof Muller-Hinton agar (MHA) at 55°C, inoculated with 1mL of the microbial culture (10^6 CFU/Ml), was poured in sterile Petri dish and left to solidify. A sterile filter paper disc impregnated with solution of the compound under testing(100µg/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 innoculum of 106 CFU in each tube. The tubes were incubated overnight at 37°C.The inhibitory concentration was determined and compared to that of Amphotricin B, Clotrimazole and Ketoconazole.

RESULTS AND DISCUSSION

Chemistry

The starting material 6-methoxy-1-tetralone **I,** comprises a cyclic buterophenone which is suitable to furnish the versatile intermediateα,β-unsaturated ketones, the chalcones **IIa-f**. These chalcones were synthesized via Claisen-Schemidt 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 **I** with different aromatic aldehydes namely, *p*-chlorobenzaldehyde, *p*-dimethyl-aminobenzaldehyde, 3,4-dimethoxybenzaldehyde, cinnamaldehyde, *p*-nitrobenzaldhyde and *m*-methoxy-benzaldehye, in the presence of 10% potassium hydroxide uneventfully afforded the corresponding 2-[(substituted phenyl)methylene]-6-methoxy-3,4-dihydro1(2*H*)-naphthalenes **IIa-f** in 65-90% yields. The structures of compounds **IIa-f** were confirmed by micro-analytical analyses and spectral data (IR, ^{1}H-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 ^{1}H-NMR spectrum of **IIa**, as an example, revealed two triplets at δ 2.91, 3.14 ppm referring to the C_3 and C_4 alicyclic methylene protons, two singlet signals at δ 3.93, 6.71 ppm attributed to OCH_3, and the vinylic 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 formulae

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[40,41]. 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 3344and 1668 cm^{-1}, respectively in the IR spectrum of compound **IIIb** agreed with the proposed structure. In addition, the ^{1}H-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 **IIIb** 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 arylidinecyanoacetate, arylidinethiocyanoacetamide or arylidinemalononitrile 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 ^{1}H-NMR spectrum of compound **VIa** displayed a broad D_2O 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.

Table1: Inhibition zones (mm) against the test organisms.

Compound	*B. subtilis*	*S. aureus*	*E. Coli*	*C. albicans*
IX	**18****	**11***	**--**	**16****
X	**16****	**14***	**16****	**19****
XI_a	**--**	**--**	**--**	**--**
XIb	**--**	**--**	**--**	**--**
Amoxicillin	**10**	**--**	**8**	**--**

*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 ^{1}H-NMR spectrum of the same compound exhibited a singlet signal due to NH proton (D_2O exchangeable) at δ 9.14 ppm, in addition to the expected two alicyclic methylenes, methoxy and aromatic protons atδ 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-dimethylaminobenzaldehydethiosemicarbaz- one, 3,4-dimethoxy- benzaldehydethiosemicarbazone, cinnamaldehydethiosemicarbazone,and 4-nitrobenz-aldehydethiosemicarbazone 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. ^{1}H-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%

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. *Staphelococcus 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[44] using 100 µL of suspension containing 1 $x10^8$ CFU/mL of the pathological tested bacteria and 1 $x10^6$ 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 [45].The diameter of inhibition zones of the screened compounds are recorded in table (**1)**.

According to table **(1)**, it could be investigated thatthe 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 *Staphelococcus 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 (4-0.05µg/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 naphthaleno[*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.

Acknowledgement

The authors are grateful to Dr. Hesham Radwan and Dr. Mohammed Emara from Microbiology department in faculty of Pharmacy, Helwan University for carrying out the antimicrobial screening.

Conflict of Interest

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

REFERENCES

1. Davies, J.; Davies, D. Origins and Evolution of Antibiotic Resistance. *Microbiol. Mol. Biol. Rev.* **2010**, *74*, 417–433.
2. Tenover, F.; McDonald, L. Vancomycin-resistant staphylococci and enterococci: epidemiology and control.*Curr. Opin. Infect. Dis.* **2005**, *18*, 300-305.
3. Khan, M.; Alam, M.; Rashid, M.; Chowdhury, R. A new structural alternative in benzo[b]furans for antimicrobial activity. *Bioorg. Med. Chem*. **2005,** *13*, 4796-4805.
4. Malecki, N.; Carato, P.; Rigo, G.; Goossens, J.; Houssin, R.; Bailly, C.; Henichart, J. Synthesis of condensed quinolines and quinazolines as DNA ligands. *Bioorg. Med. Chem*. **2004**, *12*, 641–647.
5. Gundla, R.; Kazemi, R.; Sanam, R.; Muttineni, R.; Sarma, J.; Dayam, R.; Neamati, N. Discovery of novel small-molecule inhibitors of human epidermal growth factor receptor-2: Combined ligand and target-based approach. *J. Med. Chem*. **2008**, *51*, 3367–3377.
6. Rewcastle, G. W.; Palmer, B. D.; Bridges, A. J.; Showalter, H.; Sun, L.; Nelson, J.; McMichael, A.; Kraker, A.; Fry, D.; Denny, W. Tyrosine kinase inhibitors. Synthesis and evaluation of fused tricyclic quinazoline analogues as ATP site inhibitors of the tyrosine kinase activity of the epidermal growth factor receptor. *J. Med. Chem*. **1996**, *39*, 918–928.
7. Luth, A.; Lowe, W. Syntheses of 4-(indole-3-yl) quinazolines: A new class of epidermal growth factor receptor tyrosine kinase inhibitors. *Eur. J. Med. Chem.* **2008**, *43*, 1478–1488.
8. Colotta, V.; Catarzi, D.; Varano, F.; Lenzi, O.; Filacchioni, G.; Costagli, C.; Galli, A.; Ghelardini, C.; Galeotti, N.; Gratteri, P.;Sgrignani, J. Structural Investigation of the 7-Chloro-3-hydroxy-

1Hquinazoline-2,4-dione. Scaffold to obtain AMPA and Kainate Receptor Selective Antagonists. Synthesis, Pharmacological, and Molecular Modeling Studies. *J. Med. Chem*. **2006**, *49*, 6015–6026.
9. Foster, B. A.; Coffrey, H.A.; Morin, M.J.; Rastinejad, F. Pharmacological rescue of mutant p53 conformation and function. *Science* **1999**, *286*, 2507–2510.
10. Herget, T.; Freitag, M.; Morbitzer, M.; Kupfer, R.; Stamminger, T.; Marschall, M. Novel chemical class of pUL97 protein kinase-specific inhibitors with strong anticytomegaloviral activity. *Antimicrob. Agents Chemother*. **2004**, *48*, 4154–4162.
11. Martin, T.; Wheeler, A.; Majewski, R.; Corrigan, J. Sulfanilamidoquinazolines. *J. Med. Chem*. **1964**, *7*, 812–814.
12. Waisser, K.; Gregor, J.; Dostal, H.; Kunes, J.; Kubicova, L.; Klimesova, V.; Kaustova, J. Influence of the replacement of the oxo function with the thioxo group on the antimycobacterial activity of 3-aryl-6,8-dichloro-2H-1,3-benzoxazine-2,4(3H)-diones and 3-arylquinazoline-2,4(1H,3H)-diones. *Farmaco.***2001**, *56*, 803–807.
13. Kunes, J.; Bazant, J.; Pour, M.; Waisser, K.; Slosarek, M.; Janota, J. Quinazoline derivatives with antitubercular activity. *Farmaco*. **2000**, *55*, 725–729.
14. Fry, D.W.; Kraker, A.J.; McMichael, A.; Ambroso, L.A.; Nelson, J.M.; Leopold, W.R.; Connors, R.W.; Bridges, A.J. A specific inhibitor of the epidermal growth factor receptor tyrosine kinase. *Science*. **1994**, *265*, 1093–1095.
15. Asif, M. Chemical Characteristics, Synthetic Methods, and Biological Potential of Quinazoline and Quinazolinone Derivatives. *Int. J. Med Chem.* **2014**, *1*-27.
16. Solomon, V.; Lee, H. Quinoline as a privileged scaffold in cancer drug discovery. *Curr. Med. Chem*. **2011**, *18*, 1488-1508.
17. Williams, P.; Sorribas, A.; Howes M.J.R. Natural products as a source of Alzheimer's drug leads. *Nat. Prod. Rep*. **2011**, *28*, 48–77.
18. Chen, Y. L.; Fang, K.C.; Sheu, J.Y.; Hsu, S.L.; Tzeng, C.C. Synthesis and Antibacterial Evaluation of Certain Quinolone Derivatives. *J. Med. Chem*. **2001**, *44*, 2374-2377.
19. Zajdel, P.; Partyka, A.; Marciniec, K.; Bojarski, A.J.; Pawlowski, M.; Wesolowska, A. Quinoline- and isoquinoline-sulfonamide analogs of aripiprazole: novel antipsychotic agents? *Future Med. Chem*. **2014**, *6*, 57–75.
20. Mukherjee, S.; Pal, M. Quinolines: a new hope against inflammation. *Drug Discov. Today*, **2013**, *18*, 389–398.
21. Mukherjee, S.; Pal, M. Medicinal chemistry of quinolines as emerging anti-inflammatory agents: an overview. *Curr. Med. Chem*., **2013**, *20*, 4386-4410.
22. Orhan, M.; Tekiner, B. Suzen, S. Recent Studies of Antioxidant Quinoline Derivatives. *Mini-Rev. Med. Chem*. **2013**, *13*, 365–372.
23. Musiol, R. Quinoline-Based HIV Integrase Inhibitors. *Curr. Pharm. Des.***2013**, *19*, 1835–1849.
24. Musiol, R.; Serda, M.; Hensel-Bielowka, S.; Polanski, J. Quinoline-Based Antifungals. *Curr. Med. Chem*. **2010**, *17*, 1960–1973.
25. Costedoat-Chalumeau, N.; Dunogue, B.; Morel, N. Le Guern, V.; Guettrot-Imbert, G. Hydroxychloroquine: a multifaceted treatment in lupus. *Presse Med*. **2014**, *43*, 167–180.
26. Bongarzone, S.; Bolognesi, M.L. The concept of privileged structures in rational drug design: focus on acridine and quinoline scaffolds in neurodegenerative and protozoan diseases. *Expert Opin. Drug Discov*. **2011**, *6*, 251–268.
27. Keri, R.S.; Patil, S.A. Quinoline: A promising anti-tubercular target. *Biomed. Pharmacother*. **2014**, *68*, 1161–1175.
28. Singh, S.; Kaur, G.; Mangla, V.; Gupta, M.K. Quinoline and quinolones: promising scaffolds for future antimycobacterial agents. *J. Enzyme Inhib. Med. Chem.*, **2014**, *30*, 492-504.
29. Bawa, S.; Kumar, S.; Drabu, S.; Kumar, R. Structural modifications of quinoline-based antimalarial agents: Recent developments. *J. Pharm. Bio. Allied Sci*. **2010**, *2*, 64–71.
30. Gryzło, B.; Kulig, K. Quinoline: a Promising Fragment in the Search for New Antimalarials. *Mini-Rev. Med. Chem*. **2014**, *14*, 332-*344.*
31. Afzal, O.; Kumar, S.; Haider, M.R.; Ali, M.R.; Kumar, R.; Jaggi, M.; Bawa, S. A review on anticancer potential of bioactive heterocyclequinoline. *Eur. J. Med. Chem*. **2105**, *97*, 871-910.
32. Vlahopoulos, S.; Critselis, E.; F Voutsas, I.; A Perez, S.; Moschovi, M.; Baxevanis, C.; P Chrousos, G. New Use for Old Drugs? Prospective Targets of Chloroquines in Cancer Therapy. *Curr. Drug Targets* **2014**, *15*, 843–851.
33. Bharate, J. B.; Vishwakarma, R.A.; Bharate, S.B. Metal-free domino one-pot protocols for quinolone synthesis. *RSC Adv*. **2015**, *5*, 42020–42053
34. Al-Tel T. H., Al-Qawasmeh R. A.; Zaarour R. Design, synthesis and in vitro antimicrobial evaluation of novel Imidazo[1,2-a]pyridine and imidazo[2,1-b][1,3]benzothiazole motifs. *Eur. J. Med. Chem*. **2011**, *46*, 1874-1881.
35. Kamal, A.; Srikanth, Y. V. V.; Khan, M. N. A., Ashraf, M., Reddy, M. K., Sultana, F., Kaur, T., Chashoo, G., Suri, N., Sehar, I. and Wani, Z.A... 2-

Anilinonicotinyl linked 2-aminobenzothiazoles and [1,2,4]triazolo[1,5-b] [1,2,4]benzothiadiazine Conjugates as potential mitochondrial apoptotic inducers. *Bioorg. Med. Chem.* **2011**, *19*, 7136-7150.

36. Mortimer, C. G.; Wells, G.; Crochard, J.P.; Stone, E.; Bradshaw, T.; Stevens, M.; Westwell, A.D. Antitumourbenzothiazoles. 26. 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole (GW 610, NSC 721648), a simple fluorinated 2-arylbenzothiazole, shows potent and selective inhibitory activity against lung, colon, and breast cancer cell lines. *J. Med. Chem.* **2006**; *49*, 179-185.
37. Lee, Y. R.; Jin, G. H.; Lee, S.M.;Park, J.W., Ryu, J. H., Jeon, R. and Park, B.H.,. Inhibition of TNF-alpha-mediated inflammatory responses by a benzodioxolylacetylamino-linked benzothiazole analog in human fibroblast-like synoviocytes. *BiochemBiophys Res. Commun*. **2011**; *408*, 625-629.
38. Kamal, A.; Syed, M. A. H.; Mohammed, S.M. Therapeutic potential of benzothiazoles: a patent review (2010-2014). *Expert Opin. Ther. Patents* **2015**, *25*, 335-349.
39. Upadhayaya, R. S.; Sinha, N.; Jain, S.; Kishore, N.; Chandra, R.; Arora, S. K. Optically active antifungal azoles: synthesis and antifungal activity of (2R 2-(2,4-difluorophenyl)-3-(5-{2-[4-aryl-piperazin-1-yl]-ethyl}-tetrazol-2-yl/1-yl)-1-[1,2,4]-triazol-1-yl-butan-2-ol. *Bioorg. Med. Chem.* **2004**, *12*, 2225–2238.
40. Powers, D.G.; Casebier, D.S.; Fokas, D; Ryan, W.J.; Troth, J.R.; Coffen, D.L. Automated Parallel Synthesis of Chalcone-Based Screening Libraries. *Tetrahedron*. **1998**, *54*, 4085-4096.
41. Kim, S. H.; Ahn, C. H.; Keum, S. R.; Koh, K. Synthesis and properties of spiroxazine polymer having photocrosslinkable chalcone moiety. *Dyes and Pigments* **2005**, *65*, 179-182.
42. Yadav, P. P.; Gupta. P.; Chaturvedi, A.K.; Shukla, P.K.; Maurya, R. Synthesis of 4-hydroxy-1-methylindole and benzo[b]-thiophen-4-ol base unnatural flavonoids as new class of anti-microbial agents. *Bioorg. Med. Chem*., **2005,** *13*, 1497–1505.
43. Kibou, Z.; Cheikh, N.; Villemin, D.; Choukchou-Braham, N.; Mostefa-Kara, B.; Benabdallah, M. A Simple and Efficient Procedure for a 2-Pyridones Synthesis under Solvent-Free Conditions. *Int. J. Org. Chem.* **2011**, *1*, 242-249.
44. Madigan, M. T.;Martinko, J.M.; Parker, J. Brock Biology of Microbiology. Tenth edition. Pearson Education, Inc. New Jersey, **2003**, p. 704.
45. Ozden, S.; Atabey, D.; Yıldızb, S.; Goker, H. Synthesis and potent antimicrobial activity of some novel methyl or ethyl benzimidazole-5-carboxylates derivatives carrying amide or amidine groups. *Bioorg. Med. Chem.*, **2005**, *13*, 1587–1597.