Design – Syntheses, Characterization and Evaluation Antimicrobial Activity for Some azobenzen-p, p'-disubstituted with (3, O), (3, N-) substitute, (3, H) -quinazolin-4-one-2yl and 4-substituted quinazolin-2yl moieties

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Abstract: Two of 3, O-substituted quinazoline-4-one namely azobenzen-p, p'-di[3, O-benzyl-4 (3H) quinazolin-4-one-2yl], and azobenzen-p, p'-di[3, O-acetyl-4 (3H) quinazolin-4-one-2yl], were synthesized from azobenzen-p, p'-di[3-hydroxy-4 (3H) quinazolin-4-one-2yl]. Two of 3-N-substituted quinazoline-4-one namely azobenzen-p, p'-di[3, N-benzen sulphonylamide-4 (3H) quinazolin-4-one-2yl], and azobenzen-p, p'-di[3, N-(4'-nitrofururylidene-2'-yl imino) -4 (3H) quinazolin-4-one-2yl], were synthesis from azobenzen-p, p'-di[3-amino-4 (3H) quinazolin-4-one-2yl], azobenzen-p, p'-di[3-hydroxy-4 (3H) quinazolin-4-one-2yl], was synthesized from azobenzen-p, p'-di (3, 1-benzoazine-4-one-2yl], which was used for synthesis azobenzen-p, p'-di[4-chloro-quinazolin-2yl], while its treatment with p-toluidine and ethylene diamine give azobenzen-p, p'-di[4-N-toludino-quinazolin-2yl], and azobenzen-p, p'-di[4-N-aminoethylamine-quinazolin-2yl] respectively. All synthesized compounds characterized by FTIR, 1HNMR, 13CNMR and mass spectral analyses. All synthesized compounds, were examined as antibacterial agents against gm (+ve and –ve) bacteria, and antifungal agents. Results showed abroad extended excellent to moderate effects as antibacterial and antifungal agents.

Keywords: di-substituted-quinazolinone, antibacterial, antifungal

1. Introduction

One of the most important features in 3, 1-benzoaxazin-4-ones chemistry is their uses as starting materials key for further transformations; they are indeed useful intermediates in organic synthesis [1-7]. Its reaction with nitrogen nucleophiles gives 4 (3H) quinazolinones [8-9]. The quinazoline moiety is an important pharmacophore showing many types of pharmacological activities, the quinazolines are considered to be "privileged structure" for drug development [10-12]. They also exhibit a wide range of activities [13-15]: such as anticonvulsant, anti-inflammatory, anti-malarial, anti-sedative, Analgesic, anti-oxidant, anti-cancer, anti-microbial, anti-bacterial, anti-fungal, anti-mycobacterial, anheimlatic, muscle relaxant, anti- hyperlipidemic, anti-tubercular, anti-tumor, hypotensive activities [16-29]. also quinazoline and its derivatives are very important and vital group of chemotherapeutical drugs such as anti-histamine, anti-allergy and anti-diabetic, as well as quinazolinone and its derivatives exhibited a good activity as anti-fibrillatory [30-32]. Quinazolinone moiety is present in many commercialized drugs such as Albacazolone, Gifitinin [33-36]. Besides several quinazoline derived clinical candidates are in various stages of development [37].

2. Material and Methods

1- Syntheses of azobenzen-p, p’-di[3-substituted-4 (3H) -quinazolinone-2yl] [38]:

A mixture of azobenzen-p, p'-di[3, 1-benzoazine-4-one-2yl] (0.472gm: 0.001 mol), and amino moieties compounds, like, hydroxylamine hydrochloride, hydrazine hydrate (0.002 mol), DMF (25ml), were refluxed for a time [mentioned in table (1)], until completion of reactions were monitored by TLC using petroleum ether: ethyl acetate [3:2] eluent. Solids were separated, filtered and purified by crystallization from DMF, to give azobenzen-p, p'-di[3-substituted -4 (3H) -quinazolinone-2yl][1, 2].

Table 1: details of azobenzene-p, p’-di[3 (substituted) - 4 (3H) quinazolinone-2yl] compounds [1, 2]

<table>
<thead>
<tr>
<th>No.</th>
<th>Name of compounds</th>
<th>Weight of product</th>
<th>Yield %</th>
<th>color</th>
<th>m.p C</th>
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<td>1</td>
<td>Azobenzen-p, p’-di[3-hydroxy-4 (3H)] [quinazolinone-2yl]</td>
<td>0.4 gm</td>
<td>78</td>
<td>Pale orange</td>
<td>272</td>
</tr>
<tr>
<td>2</td>
<td>Azobenzen-p, p’-di[3-amino-4 (3H)] [quinazolinone-2yl]</td>
<td>0.53</td>
<td>88</td>
<td>yellow</td>
<td>340</td>
</tr>
</tbody>
</table>
2- Synthesis of azobenzen-p, p'-di[3, O-substituted-4 (3H) quinazolinone-2yl][1a, 1b]:

To a solution of azobenzen-p, p'-[3-hydroxy-4 (3H) -quinazolinone-2yl][1] (0.5 gm, 0.001 mol), in DMF (20ml), freshly distilled Acetyl chloride 1.56ml, or benzy1 chloride 0.25ml equivalent 0.002mol), and sodium hydroxide (0.1gm), were added. Reaction mixture was refluxed for 3hrs, until completion of reaction which was monitored by TLC using petroleum ether:ethyl acetate [3:2] eluent. Precipitate was formed, filtered and washed with distilled water, recrystallized from DMF, to give compound [a], 0.41gm, yield; 60%, m.p. 218-220°C, and compound [b], 0.38gm, yield; 55.71%, m.p. 249-251°C respectively.

3- Synthesis of azobenzen-p, p'-di[3, N-substituted-4 (3H) quinazolinone-2yl][2a, 2b]:

A- To a solution of azobenzen-p, p'-di[3-amino-4 (3H) quinazolinone-2yl][2] (0.5gm, 0.001mol), in DMF (10ml), containing dry pyridine (3ml), benzenesulfonyl chloride, (0.2ml, 0.002mol), was added in small portions, reaction mixture was refluxed for 6hrs, until completion of reaction which was monitored by TLC using petroleum ether: ethyl acetate [3:2] eluent. Reaction mixture was cooled, poured slowly into stirred ice-cold water, and kept in refrigerator for 1/2h. The precipitate was formed, filtered, washed with distilled water and dried. Then recrystallized from DMF, to give compound [2a], 0.32gm, yield; 42%, m.p. 301-303°C.

B- To a stirred solution of azobenzen-p, p'-di[3-amino-4 (3H) quinazolinone-2yl] (0.5gm, 0.001mol), in DMF (20ml), glacial acetic acid (3drops). A solution of 5-nitro-2-furaldehyde (0.274gm, 0.002mol) in ethanol (10ml), was added slowly. Reaction mixture was stirred for 8hrs, until completion of reaction which was monitored by TLC using petroleum ether: ethyl acetate [3:2]eluent. Precipitate was formed, filtered and washed with distilled water, recrystallized from DMSO, to give compound [2b], 0.38gm, yield; 52%, m.p. 211-213°C.

4- Synthesis of azobenzen-p, p'-di[3-hyrdro-4-quinazolinone-2yl] [3]:

A mixture azobenzen-p, p'-di[3, 1-benzoxazine-4-one-2yl][3] (0.472gm, 0.001mol) in DMF (20ml), ammonium acetate (0.154gm, 0.002mol), ammonium hydroxide (38%), (4mL) and 10% sodium hydroxide (5mL), pyridine (15mL), was heated under reflux for 8hrs, until completion of reaction which was monitored by TLC using petroleum ether: ethyl acetate [3:2] eluent, and then left to cold. Reaction mixture was then triturated with cold distilled water (100mL) and neutralized with 1N HCl (5mL), resulting precipitate was collected by filtration, washed with water, dried and recrystallized from DMF, to give compound [3], 0.36gm, yield; 76%, m.p. 190-192°C

5- Synthesis of azobenzen-p, p'-di[4-chloro-quinazolin-2yl] [4]:

A mixture of azobenzen-p, p'-di[3-hyrdro-4H-quinazolinone-2yl ] [3] (0.47gm, 0.001mol), phosphorouspentachloride (0.416gm, 0.002mol), phosphorousoxychloride (20mL), containing dry pyridine (5ml), was heated on a water bath for 6hrs, until completion of reaction which was monitored by TLC using petroleum ether: ethyl acetate [3:2] eluent. Reaction mixture was poured gradually on crashed ice. The separated solid was filtered off, dried then recrystallized from DMF to give compound [4], 0.35gm, yield; 69%, m.p. 236°C.

6- Synthesis of azobenzen-p, p'-di[4-substituted-quinazolin-2yl] [4a, 4b]:

A mixture of azobenzen-p, p'-di[4-chloro-quinazoline-2yl][4] (0.507gm, 0.001mol) and amino-moieties like [p-toluidine (2.1gm) or 1, 2-diaminoethanedihydrochloride (0.27gm) equivalent to (0.002mol)] respectively in DMF (20mL) were refluxed for 6hrs, until completion of reaction which was monitored by TLC using petroleum ether: ethyl acetate [3:2] eluent. Separated solid was filtered off, dried then recrystallized from DMF to give compound [4a], 0.4gm, yield 61.7%, m.p.285°C and compound [4b] 0.38gm, yield 69.4%, m.p.307°C respectively.

3. Result and Discussion

Chemistry of quinazoline, quinazolin-4-one and their derivatives have much considerable importance, due to effectiveness in biological and pharmacological fields. Because off these reason, we design to synthesis some of new (3, O-), (3, N-) substituted quinazolin-4-one-2yl and 4-substituted quinazoline-2yl moieties, substituted at (p,p') - positions of bridged azobenzene molecule.

A. First: azobenzen-p, p'-di[3-hydroxy-4-3H quinazolin-4-one-2yl], was synthesized and characterized as in published paper [38]

Second: Synthesis of azobenzen-p, p'-di[3, O-substituted-4 (3H) quinazolinone-2yl][1a, 1b]:

Condensation of azobenzen-p, p'-di[3-hydroxy-4 (3H) quinazolinone-2yl][1] with benzyl chloride or acetyl chloride in a molar ratio (1:2), give azobenzen-p, p'-di[3, O-benzyl-4 (3H) quinazolinone-2yl][1a] and azobenzen-p, p'-di[3, O-acetyl-4 (3H) quinazolinone-2yl][1b] respectively. These compounds are characterized by FTIR, 1H NMR, and 13C NMR spectral analysis. FTIR- spectral analysis of compounds

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[1a], showed stretching band of azo (N=N) group at 1446 cm⁻¹, beside quinazoline ring stretching C=O and C=N bands at 1670, 1620 cm⁻¹ respectively. But ¹H NMR- spectrum of compounds [1a], showed quinazoline ring and phenyl ring protons as multiple (26H) protons, at δ (6.9 - 8.7) ppm, beside two methylene protons as (4H) protons at δ (3.5) ppm. While ¹³C NMR- spectrum of this compound showed quinazoline carbon as aromatic, (C=O), (C=N) carbons signal at δ (109 - 145), (168), (153) ppm respectively, beside methylene (CH₂) carbon at δ (71) ppm [39]. FTIR- spectral analysis of compound [1b], showed carbonyl of (CH₃=CO) bands and azo (-N=N-) stretching bands at (1712, 1473) cm⁻¹, as well as to quinazoline (C=O), (C=N) stretching bands at (1674 and 1604) cm⁻¹ respectively. ¹H NMR- spectrum of compound [1b], showed quinazoline ring protons as a multiple (16H) at δ (6.7 - 8.2) ppm, and methyl protons of acetyl groups as a singlet signal at δ (3.2) ppm. ¹³C NMR- spectrum of this compound showed quinazoline ring as aromatic carbonyl carbon of (C=O), and (C=N) carbons as a multiple signals at δ (111 - 145) ppm, and singlet signals at δ (165 and 153) ppm respectively, beside carbon signal of methyl group at δ (70) ppm.

B. First: azobenzen-p, p'-di[3-amino-4- (3H) quinazolin-4-one-2yl], was synthesized and characterized as in published paper [38].

Second: Synthesis of azobenzen-p, p'-di[3, N-substituted-4 (3H) quinazolinone-2yl][2a, 2b]:

Condensation of azobenzen-p, p'-di[3, 1-benzoxazin-4-one-2yl] with excess of ammonia and ammonium acetate in DMF, in a molar ratio (1:2), gave azobenzen-p, p'-di[3-hydro- (4H) -quinazolinone-2yl] [3], which was characterized by FTIR, ¹HNMR, ¹³CNMR, and mass spectral analysis. FTIR- spectral analysis of compound [3], showed azo-group (N=N) at (1452) cm⁻¹, beside 3-hydro-4-quinazolinone ring stretching bands (NH), (C=O), and (C=N), at (3267, 1661, 1600 cm⁻¹) respectively. ¹H NMR- spectrum of this compound, showed aromatic (CH), and (NH) quinazoline protons as a multiplet signals of (18H) at (6.9 - 8.8) ppm. While ¹³C NMR-spectrum of compound [3], showed aromatic carbon of quinazoline (C=O), and azomethine (C=N) carbons as a multiplet signals at δ (115 - 143), singlet signal at (172), and (153) ppm respectively. Mass spectral analysis of compound [3], showed M⁺²² ion at m/z (470) in the extensional part of this spectrum (using NL:8.01E6).

Azobenzen-p, p'-di[3, N-benzenesulphonamido-4 (3H) quinazolinone-2yl] [2a], was synthesized by condensation of azobenzen-p, p'-di[3-amino-4 (3H) quinazolinone-2yl] [2] with benzenesulphonyl chloride in a molar ratio (1:2), characterized by FTIR, ¹H NMR, and ¹³C NMR spectral analysis. FTIR- spectral analysis of this compound [2a] showed stretching frequency of quinazolin ring C=O and C=N bands at 1674 and 1620 cm⁻¹ respectively, beside sulphonamido (NH) and azo (N=N) stretching bands at 3271 and 1446 cm⁻¹ respectively. ¹H NMR- spectrum of this compound, showed all aromatic (-CH) and (-NH) sulphonamido proton as a cluster of multiple (28 H) signals at a range δ (6.8 - 9.1) ppm. While ¹³C NMR- spectrum of compound [2a] showed aromatic (-CH), carbonyl carbon (C=O), and azomethine (C=N) carbon signals of quinazolin ring as multiple at δ (117 - 132), singlet signal at δ (172) and (153) ppm respectively.

While Azobenzen-p, p'-di[3, N (4'-nitrofururyldin-2'-yl)-imino] -4 (3H) -quinazolinone-2yl] [2b], FTIR- spectrum, showed stretching frequency of quinazolin ring C=O and C=N bands at 1635 and 1581 cm⁻¹ respectively, as well as stretching bands of azo N=N group at 1442 cm⁻¹, and asymmetric and symmetrical stretching bands of NO₂ at 1508, 1338 cm⁻¹ respectively.

C. Synthesis of azobenzen-p, p'-di[3-hydro- (4H) -quinazolinone-2yl] [3]:

![Condensation of azobenzen-p, p'-di[3, 1-benzoxazin-4-one-2yl] with excess of ammonia and ammonium acetate in DMF, in a molar ratio (1:2), gave azobenzen-p, p'-di[3-hydro- (4H) -quinazolinone-2yl] [3], which was characterized by FTIR, ¹HNMR, ¹³CNMR, and mass spectral analysis. FTIR- spectral analysis of compound [3], showed azo-group (N=N) at (1452) cm⁻¹, beside 3-hydro-4-quinazolinone ring stretching bands (NH), (C=O), and (C=N), at (3267, 1661, 1600 cm⁻¹) respectively. ¹H NMR- spectrum of this compound, showed aromatic (CH), and (NH) quinazoline protons as a multiplet signals of (18H) at (6.9 - 8.8) ppm. While ¹³C NMR-spectrum of compound [3], showed aromatic carbon of quinazolinone (C=O), and azomethine (C=N) carbons as a multiplet signals at δ (115 - 143), singlet signal at (172), and (153) ppm respectively. Mass spectral analysis of compound [3], showed M⁺²² ion at m/z (470) in the extensional part of this spectrum (using NL:8.01E6).]
D- Synthesis of azobenzen-p, p’-di[4-chloro-quinazolin-2yl][4]:

FTIR- spectral analysis of compound [4a], showed (NH) stretching bands of amino group (NH) and azo (N=N) at (3200, 1454) cm$^{-1}$ respectively, beside quinazolin (C=N) stretching bands at (1631, 1543) cm$^{-1}$ respectively. While $^{1}$H NMR- spectrum of this compound [4a], showed singlet signal of methyl protons at $\delta$ (4.01) ppm, as well as aromatic ring (CH) proton and amino proton as a multiplet signal of (26H) proton at $\delta$ (6.8 - 8.9) ppm. But $^{13}$C NMR- spectrum of this compound showed methyl carbon (CH$_3$) as a singlet signal at $\delta$ (93) ppm, beside quinazolin ring (aromatic carbon and azomethine carbon (C=N) carbon) as a multiplet signals at $\delta$ (117 - 145 and 153) ppm respectively.

FTIR-spectrum of compound [4b], showed both (NH) and (NH$_3$) stretching bands at 3481-3431, 3282 cm$^{-1}$ and azo stretching band (N=N) at 1431 cm$^{-1}$, beside quinazolin ring azomethine (C=N) at 1621, 1598 cm$^{-1}$ respectively.

E- Synthesis of azobenzen-p, p’-di[4-substituted-quinazolin-2yl][4a, 4b]:

Substitution reaction of chlorine in azobenzen-p, p’-di[4-chloro-quinazolin-2yl] [4], with p-toluidine or ethylenediamine, gave azobenzen-p, p’-di[4, N-toluidino-quinazolin-2yl] [4a] and azobenzen-p, p’-di[4, N-aminoethylamine-quinazolin-2yl] [4b] respectively. Azobenzen-p, p’-di[4, N-toluidino-quinazolin-2yl] [4a], was characterized by FTIR, $^{1}$H NMR and $^{13}$C NMR spectral analysis.

F- Anti-microbial studies:

Synthetic compounds [1, 1 (a, b), 2, 2 (a, b), 3, 4, 4 (a, b) ], were examined as antibacterial agents against gm (+ve) Staphylococcus aurous, Bacillus bacteria, and gm (-ve) Escherichia coli, Klebsiella pneumonia bacteria, in comparison with effect of Cephalexin, Amoxicillin, Tetracycline Lincomycin antibiotics. Also these were examined as antifungal agents against Aspergillus flavs and Penecillium fungi in comparison with the effect of Nystatin and Fluconazole antifungal treatments.

According to the results given in Table (2), following observation would be deduced:

First: All synthesized compounds, except (1b), were found to have excellent effect on gm (+ve) Bacillus bacteria in comparison with antibiotics.

Second: All synthesized compounds, were found to have very good to good effect on gm (+ve) Staphylococcus aurous bacteria, specially compounds (1, 1b, 2, 2a & 3), in comparison with antibiotics.

Third: All synthesized compounds, except (1, 2, 4), were found to have good to very good effect on gm (-ve) Escherichia coli bacteria, specially (1b and 2b) in comparison with antibiotics.

Fourth: All synthesized compounds, except (1b, 2b, 4), were found to have moderate effect on gm (-ve) Klebsiella pneumonia bacteria in comparison with antibiotics.

Fifth: All synthesized compounds, were found to have moderate effect on Aspergillus flavs fungi, specially compound [3], in comparison with antifungal treatments.

Sixth: All synthesized compounds, were found to have moderate effect on Pencillium fungi, specially compound [3, 4], in comparison with antifungal treatments.


<table>
<thead>
<tr>
<th>No.</th>
<th>Structure of compounds</th>
<th>Mean of Inhibition zone Diameter (mm)</th>
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<tr>
<td>1</td>
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<td>1a</td>
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References


Author Profile

Dr. Zakaria H. Aiube, received M.Sc. degree in organic chemistry from Baghdad university / Iraq during 1974-1976, and received Ph.D. degree in organo-silicon chemistry from Sussex university/ united kingdom during 1980-1985. I have many researches in the following field. Sterically reaction mechanisms, organic syntheses and antimicrobial studies, inventions in petroleum– industrial fields. I was teaches many courses for under graduate and post graduate students in fields: organic reaction mechanism. Spectroscopic and characterization of organic compounds, natural products (Alkaloids).

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1466