Design, Synthesis, and Antioxidant Evaluation of Novel 6-Iodo-3-Substituted-Quinazolin-4(3H)-on-2-yl Benzoic Acid

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Abstract

A new series of 6-iodo-2-phenyl-3-substituted-quinazolin-4(3H)-one derivatives were synthesized, evaluated for their anticonvulsant activity against pentylenetetrazole (PTZ)-induced seizures and maximal electroshock test and compared with the reference drugs phenobarbital sodium and methaqualone. The data obtained from the molecular modeling were correlated with those obtained from the biological screening. Compounds 3a, 3b, 5a and 7a showed the highest insectical activities of this series with relatively low neurotoxicity and low toxicity in the median lethal dose test when compared with the reference drugs. The obtained results proved that the most active compounds could be a useful model for future design, adaptation and investigation to construct more active analogs.

Key words:Isoindoline, Antioxidant, Synthesis, 6-iodo-3-substituted-quinazolin-4(3H)-on-2-yl benzoic acid


1. Introduction

Quinazolin-4(3H)-ones and their derivatives constitute an important class of heterocyclic compounds and are shown to have potent CNS activities such as anticonvulsant1–6 and CNS depressant. A literature survey revealed that the presence of an aromatic or aliphatic group at position 2 and a substituted aromatic ring at position 3 are necessary requirements for the CNS depression and anticonvulsant activities.4,8 The presence of the phenyl group at second position of quinazolin-4(3H)-one was more significant than methyl and yielded more potent CNS active agents.4 The sedative-hypnotic (neurotoxicity) properties of 4(3H)-quinazolinone are well documented.9 2-Methyl-3-O-tolyl 4(3H)-quinazolinone (methaqualone) is an important landmark in the field of synthetic anticonvulsant, possesses quinazoline core which was responsible for its activity.10,11 Many quinazoline derivatives were reported as GABA-A receptor stimulants.2,4 The GABA-A receptor is an ionotropic receptor and a ligand-gated ion channel. Its endogenous ligand is \( \gamma \)-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system. Upon activation, the GABA-A receptor selectively conducts Cl through its pore, resulting in hyperpolarization of the neuron. This causes an inhibitory effect on neurotransmission by diminishing the chance of a successful action potential.2 The active site of the GABA-A receptor is the binding site for GABA and several drugs such as muscimol. The protein also contains a number of different allosteric binding sites which modulate the activity of the receptor indirectly. These allosteric sites are the targets of various other drugs, including benzodiazepines, barbiturates and ethanol.12 Methaqualone is a positive allosteric GABA-A receptor modulator. It binds to allosteric sites on the GABA-A receptor complex and affects it in a positive manner, causing increased efficiency of the main site and therefore an
indirect increase in Cl_ conductance.12 Many quinazolinones structurally related to compound methaqualone were synthesized and biologically tested for their anticonvulsant activity. None of those compounds are currently used.11,13 A persistent problem encountered with these compounds arises from the fact that, nearly every derivative tested in combined neurotoxicity and anticonvulsant screenings exhibited neurotoxicity values (TD50’s) that are less than or only slightly higher than the effective doses (ED50’s) consequently, the protective index (PI) corresponding to (TD50/ED50) is too low.14 In continuation to the efforts done toward the synthesis of potential molecules as anticonvulsant agents, our aim was to synthesize new 6-iodo-2-phenyl-3-substituted-quinazolin-4(3H)-one (5–12) derivatives and evaluate their anticonvulsant potency. It was of special importance to incorporate some moieties that were reported to potentiate the anticonvulsant activity such as pyrazoles,15,16 pyrimidones, pyrimidinethiones,17,18 pyridines,19 pyrans20 and to furnish the target compounds. Moreover, the choice of substituents was based on their relatively high lipophilicity to pass the blood–brain barrier aiming to have strong anticonvulsant activity.

2- Result and discussion

2.1 Chemistry

The sequence of reactions used in the synthesis of the target compounds is illustrated in Schemes 1–2. A new series of the title compounds incorporated into diverse N and O heterocyclic moieties were synthesized starting with anthranilic acid by its reaction with iodine in the presence of aqueous KOH to give 5-iodoanthranilic acid which treated with phthalic anhydride to afford N-(2-carboxy)benzoyl-5-iodoanthranilic acid following the reported procedures.25 Refluxing of N-(2-carboxy)benzoyl-5-iodoanthranilic acid (1) in acetic anhydride afforded 2-(6-iodo-4H-3,1-benzoxazin-4-yl)benzoic acid (2). which reacted with 4-amino benzoic acid, 2-aminopyridine, 4-anisidine and 4-aminobutanol to give the corresponding compounds, 2-(6-iodo-3-(4-aryl)-4(3H)-quinazolin-2yl) benzoic acids (3a-d). Reaction of the benzoxazinone 2 with o-tolidine (4,4-bis o-toluidine) in boiling ethanol afforded the corresponding quinazolinone (4) (Scheme 2). Also, when the reaction of bezoxazinone 2 was allowed to react with glucosamine in boiling acetic acid, it afforded pyranosylquinazolinone derivatives (5 and 6) that underwent for acetylation by acetic acid afforded triacetate derivative (6). Reaction of benzoxazinone 2 with phosphorous pentasulphide and carried out xylene, the thio derivative (7) was obtained. Moreover, Amination of the benzoxazinone 2 by thiosemicarbazide, and acetylhydrazide yielded the corresponding quinazolinone 8 and 9 respectively. On the other hand, when the benzoxazinone 3 allowed to react with hydrazine hydrate in boiling ethanol afforded quinazolinopyridazinone derivative (10) in 65% yield (Scheme 2). The reaction of compound 10 with ethylchloroacetate in the presence of excess anhydrous potassium carbonate in acetone afforded the corresponding ester 11. Furthermore, reaction of the compound 10 with phosphorous pentasulphide afforded the thio derivative 12 (Scheme 2).

2.2 Antioxidant evaluation

The oxidation test was carried out according to ASTMD-943 standard method. The oxidation cell in the static mode contained 200 ml base stock, and copper and iron wires as catalysts. The base stock sample was subjected to oxidation at 120°C with pure oxygen (99.95%) at a flow rate of 0.1 liter/hour for maximum 96 hours. The characterized compounds were added with different concentrations (200, 400 and 500 ppm). The oil samples were examined (after 24, 48, 72 and 96 hours respectively) through the change of viscosity and total acid number (TAN). The parameters
were carried out for the oxidized samples according to control of ABTS, respectively. It was interesting to study the effect of concentration of the prepared additives. Thus, three different concentrations, 200 ppm, 400 ppm, 500 ppm of each additive were used. The data in the Table 1 reveals that the most effective concentration in all cases is 200 ppm i.e. the total acid number increase by increasing the concentration of the additives. The most spirooxindoline additive were at optimum concentration correspond to 200 ppm, the order of increasing inhibition efficiency of spirooxindolines were ranked as follows: 9 > 6 > 5 > Ascorbic acid which were consistent with order of higher \( E_{\text{HOMO}} \) values.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Absorbance of samples</th>
<th>% inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control of ABTS</td>
<td>0.498</td>
<td>0%</td>
</tr>
<tr>
<td>Ascorbic-acid</td>
<td>0.219</td>
<td>56.0%</td>
</tr>
<tr>
<td>1</td>
<td>0.152</td>
<td>69.5%</td>
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<tr>
<td>2</td>
<td>0.262</td>
<td>47.4%</td>
</tr>
<tr>
<td>3a</td>
<td>0.268</td>
<td>46.2%</td>
</tr>
<tr>
<td>3b</td>
<td>0.373</td>
<td>25.1%</td>
</tr>
<tr>
<td>3c</td>
<td>0.186</td>
<td>62.6%</td>
</tr>
<tr>
<td>4</td>
<td>0.264</td>
<td>47.0%</td>
</tr>
<tr>
<td>5</td>
<td>0.079</td>
<td>84.1%</td>
</tr>
<tr>
<td>6</td>
<td>0.121</td>
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</tr>
<tr>
<td>7</td>
<td>0.133</td>
<td>73.3%</td>
</tr>
<tr>
<td>8</td>
<td>0.181</td>
<td>63.6%</td>
</tr>
<tr>
<td>9</td>
<td>0.145</td>
<td>70.9%</td>
</tr>
<tr>
<td>10</td>
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<td>41.0%</td>
</tr>
<tr>
<td>11</td>
<td>0.225</td>
<td>54.8%</td>
</tr>
<tr>
<td>12</td>
<td>0.244</td>
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<td>13</td>
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<tr>
<td>15</td>
<td>0.115</td>
<td>76.9%</td>
</tr>
<tr>
<td>16</td>
<td>0.218</td>
<td>56.2%</td>
</tr>
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</table>

2.3 Conclusion

New derivatives of 4(3H)-quinazolinones were synthesized and evaluated for their anticonvulsant activity in mice. The results of this study demonstrated that some 6-iodo-2-phenylquinazolin-4(3H)-one derivatives attached to various heterocyclic ring systems such as: pyrazoline, pyrimidin-2-one, pyrimidin-2-thione, 2 oxo(imo) pyridine and pyran at 3rdposition exhibited good anticonvulsant activity. The molecular docking was performed for all the synthesized compounds to assess their binding affinities.
3. Experimental

Melting points are uncorrected. IR spectra in KBr were recorded on Schimadzu 8201 FT spectrometer (cm⁻¹), ¹HNMR were recorded on a Varine EM-NMR spectrophotometer 300MHz using CDCl₃ as a solvent and EIMS as initial reference (δppm) and EIMS recorded on a gas chromatographic GCMS 9P1000ex Schimadzu instrument at 70 eV:

3.1 Amino-5-Iodobenzoic acid (1)

Hydrogen peroxide (98%) 2.05 mL was added to a solution of mixture of 5 g Anthranilic acid (0.01 mol) and 4.63 g Iodine (0.01 mol) in 100 mL glacial acetic acid. The reaction mixture was stirred for 5 h and poured onto water. The precipitated solid was collected by filtration, dried and crystallized from ethanol to give 3.72 g Iodo anthranilic acid in 65% yield as pink crystals: m.p. 180—220 °C; C₂H₅NO₂ MW 262.94, m/z: 262.94 (100.0%), 263.95 (7.6%) Elemental Analysis: Calc; C, 53.03; H, 3.03; I, 25.47; N, 5.62; found; C, 52.51; H, 2.89; I, 25.12; N, 5.27.

3.2 (3-Carboxybenzamido)-5-Iodobenzoic Acid (2)

A mixture of 2 g Iodo anthranilic acid (0.002 mol) and 1.8 g phthalic anhydride (0.002 mol) in 20 mL n-butanol was refluxed for 3 h. After cooling the obtained solid was collected, dried and recrystallized from n-butanol to give 1.61 g 00l-(3-carboxybenzamido)-5-iodobenzoic acid in yield 76% as deep brown crystals: m.p. 180—182 °C; C₁₅H₁₀INO₅ MW 410.96 m/z: 410.96 (100.0%), 411.96 (16.2%), 412.97 (1.2%), 412.96 (1.0%) Elemental Analysis: Calc; C, 43.82; H, 2.45; I, 30.87; N, 3.41; found; C, 43.56; H, 2.25; I, 30.63; N, 3.15.

3.3 (6-Iodo-4-oxo-4H-Benz[d][1,3]Oxazin-2-yl) Benzoic Acid (3)

A solution of 2 g 1a (0.01 mol) in 15 mL acetic anhydride was refluxed for 1 h, after cooling the obtained solid was filtered off and crystallized from ethanol to give 1.72 g 1-[6-(iodo-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)benzoic acid] in 75% yield as white crystals: m.p. 148—150 °C; C₁₅H₁₄NO₄ MW 392.95 m/z: 392.95 (100.0%), 393.95 (16.2%), 394.96 (1.2%) Elemental Analysis: Calc; C, 45.83; H, 2.05; I, 32.28; N, 3.56; found; C, 45.51; H, 1.89; I, 32.12; N, 3.27.

3.4 Compounds 4

A mixture of 1 g (0.003 mol) of benzoazone 3, and p-aminobenzoic acid, 2-amino pyridine, p-anisidine, 4-aminobutanol (0.002 mol) in 20 mL ethanol was refluxed for 2 h. After cooling the obtained solid was collected, dried and crystallized from ethanol to give 0.76 g 4.

2-(3-(4-carboxyphenyl)-6-iodo-3,4-dihydroquinazolin-2-yl) benzoic acid (4a): yield 68% as colorless crystals: m.p. 132—134 °C; C₁₂H₁₁IN₂O₄ MW 392.95 m/z: 498 (100.0%), 500 (16.2%), 394.96 (1.2%) Elemental Analysis: Calc; C, 53.03; H, 3.03; I, 25.47; N, 5.62; found; C, 52.51; H, 2.89; I, 25.12; N, 5.27.

2-(3-(2-pyridinyl)-6-iodo-3,4-dihydroquinazolin-2-yl) benzoic acid (4b): yield 68% as colorless crystals: m.p. 132—134 °C; C₁₂H₁₂IN₂O₄ MW 392.95 m/z: 498 (100.0%), 500 (16.2%), 394.96 (1.2%) Elemental Analysis: Calc; C, 53.03; H, 3.03; I, 25.47; N, 5.62; found; C, 52.51; H, 2.89; I, 25.12; N, 5.27.

2-(3-(4-methoxyphenyl)-6-iodo-3,4-dihydroquinazolin-2-yl) benzoic acid (4c): yield 68% as colorless crystals: m.p. 132—134 °C; C₁₂H₁₁IN₂O₄ MW 392.95 m/z: 498 (100.0%), 500 (16.2%), 394.96 (1.2%) Elemental Analysis: Calc; C, 53.03; H, 3.03; I, 25.47; N, 5.62; found; C, 52.51; H, 2.89; I, 25.12; N, 5.27.

2-(3-(4-carboxybutyl)-6-iodo-3,4-dihydroquinazolin-2-yl) benzoic acid (4d): yield 68% as colorless crystals: m.p. 132—134 °C; C₁₂H₁₁IN₂O₄ MW 392.95 m/z: 498 (100.0%), 500 (16.2%), 394.96 (1.2%) Elemental Analysis: Calc; C, 53.03; H, 3.03; I, 25.47; N, 5.62; found; C, 52.51; H, 2.89; I, 25.12; N, 5.27.

3-(3-(4'-amino-2,2'-dimethyl-[1,1'-biphenyl]-4-yl)-6-iodo-4-oxo-3,4-dihydroquinazolin-2-yl) benzoic acid (5): A mixture of 0.79 g o-Tolidine (0.002 mol) and 1 g 3 (0.003 mol) in 20 mL ethanol was refluxed for 2 h. After cooling the obtained solid was collected, dried and crystallized from ethanol to give 0.56 g 14 in yield 64% as colorless crystals: m.p. >300 °C;
2-(3-(((3R,4R,5S,6S)-4,5-dihydroxy-6-(hydroxymethyl) tetrahydro-2H-pyran-3-yl) amino)-6-iodo-4-oxo-3,4-dihydroquinazolin-2-yl) benzoic acid (6): A mixture of 0.87 g 2-glucosamine (0.002 mol) and 1 g 3 (0.003 mol) in 20 mL ethanol was refluxed for 2 h. After cooling the obtained solid was collected, dried and crystallized from ethanol to give 0.76 g 13 in yield 68% as colorless crystals: m.p. 180—182 °C;

2-(3-(((3R,4R,5S,6S)-4,5-dimethoxy-6-(methoxymethyl) tetrahydro-2H-pyran-3-yl) amino)-6-iodo-4-oxo-3,4-dihydroquinazolin-2-yl) benzoic acid (7): A mixture of 02 mL acetic anhydride and 1 g 3 (0.003 mol) in 20 mL ethanol was refluxed for 2 h. After cooling the obtained solid was collected, dried and crystallized from ethanol to give 0.76 g 13 in yield 68% as colorless crystals: m.p. 180—182 °C;

2-(6-iodo-4-thioxo-4H-benzo[d][1,3] thiazin-2-yl) benzoic acid (8): A mixture of 1 g 3 (0.003 mol) and 0.58 g phosphorous penta sulfide (0.003 mol) in 20 mL xylene was refluxed for 0.5 h till orange color then Filtration on hot. After cooling the obtained solid was collected, dried and crystallized from ethanol to give 0.61 g 2 in yield 76% as colorless crystals: m.p. 188—191 °C; C_{13}H_{16}INO\textsubscript{5}S\textsubscript{2} MW 425 m/z: 425 (100.0%), 426 (16.2%). Elemental Analysis: Calc; C, 42.37; H, 1.90; I, 29.84; N, 7.52, S, 15.08; found; C, 42.21; H, 1.69; I, 59.12; N, 7.32; S, 14.87.

2-(6-iodo-4-oxo-3-thioreido-3,4-dihydroquinazolin-2-yl)benzoic acid (9): A mixture of 0.73 g thio semi carbazide (0.002 mol) and 1 g 1 (0.003 mol) in 20 mL ethanol was refluxed for 2 h. After cooling the obtained solid was collected, dried and crystallized from ethanol to give 0.61 g 4 in yield 76% as colorless crystals: m.p. 168—170 °C;

2-(3-acetamido-6-iodo-4-oxo-3,4-dihydroquinazolin-2-yl) benzoic acid (10): A mixture of 0.6 g the acetic acid hydrazide (0.002 mol) and 1 g 1 (0.003 mol) in 20 mL ethanol was refluxed for 3 h. After cooling the obtained solid was collected, dried and crystallized from ethanol to give 0.61 g 4 in yield 76% as colorless crystals: m.p. 152—154 °C;

10-iodo-6H-phthalazino[1,2-b] quinazoline-5,8-dione (11): Hydrazine hydrate (98%) 0.3 mL was added to a solution of 2 g 1 (0.006 mol) in 15 mL absolute ethanol. The reaction mixture was refluxed for 3 h, after cooling the obtained solid was filtered off and recrystallized from ethanol to give 1.72 g 15 {10-iodo-6H-phthalazino[1,2-b] quinazoline-5,8-dione} in 85% yield as colorless crystals: m.p. 198—202 °C;

ethyl 2-(10-iodo-5,8-dioxo-5,8-dihydro-6H-phthalazino[1,2-b] quinazolin-6-yl) acetate (12): A mixture of quinazoline derivative 11 (0.01 mol), ethylchloroacetate (2.4 mL, 0.02 mole) and anhydrous potassium carbonate (5.5 g, 0.04 mol) in dry dioxane (50 mL) was refluxed for 24 h. The excess solvent was then removed by distillation and the residue was diluted with water. The obtained solid was filtered off and was crystallized.

10-iodo-5-thioxo-5,6-dihydro-8H-phthalazino[1,2-b] quinazolin-8-one (13): A mixture of 1 g 11 (0.003 mol) and 0.58 g phosphorous penta sulfide (0.003 mol) in 20 mL xylene was refluxed for 0.5 h till orange color then Filtration on hot. After cooling the obtained solid was collected, dried and crystallized from ethanol to give 0.61 g 2 in yield 76% as colorless crystals: m.p. 188—191 °C; C_{13}H_{16}INO\textsubscript{2}S\textsubscript{2} MW 425 m/z: 425 (100.0%), 426 (16.2%). Elemental Analysis: Calc; C, 42.37; H, 1.90; I, 29.84; N, 7.52, S, 15.08; found; C, 42.21; H, 1.69; I, 59.12; N, 7.32; S, 14.87.

References


