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Synthesis, Characterization and Biological Activity of Various Substitutedquinazolinone Derivatives Containing Dopamine Moiety

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Abstract: A Series of 3-Substituted phenyl 2-(3,4-dihydroxyphenyl ethyl amino)-6-substituted quinazolin-4-(3H) ones (4a-4h) have been synthesized by the reaction of 3-Substituted phenyl -2-methylbromo-6-substituted quinazolin-4-(3H) ones (3a-3h) with dopamine (3,4 dihydroxy phenyl ethyl amine). The biological screening showed that compound 4f namely 3-(2-Chloro phenyl)- 2-(3, 4-dihydroxyphenyl ethyl amino)-6-bromo quinazolin-4-(3H)one has shown most potent antiparkinsonian activity. The structure assignment of the new compounds based on chemical and spectroscopic evidence. The detailed synthesis spectroscopic data and pharmacological properties are reported.

Key words: Substituted quinazolinones · Dopamine · Antiparkinsonian activity and Acute toxicity

INTRODUCTION

The deficiency of dopamine in the basal ganglia of parkinsonian patients has been established as a biochemical lesion in all forms of Parkinsonism. The Levodopa (L-DOPA), a precursor of dopamine, acts on the biochemical defects of parkinsonism and is the most effective drug available for treatment of disease. However, abundance of dopa-decarboxylase in peripheral tissues has necessitated the use of large doses and prolonged use of L-DOPA for its possible entry to brain to liberate dopamine by dopa-carboxylase and there by maintaining optimal dopamine concentration for desired beneficial effect to synthesis of new heterocyclic derivatives. In side effect of dopamine to thought the different heterocyclic to possess the lesser side effect. We promoted one of the most frequently encountered heterocyclic in medicinal chemistry is quinazolin-4(3H)-one and their derivatives are known to possess numerous interesting biological properties which include antiparkinsonian [1-3] antiviral [4] antipsychotic [5] and anti-inflammatory activity [6]. In hope of getting response of quinazolinone nucleus itself, substitution of dopamine [7, 8] and different anilines. The present paper reports on the antiparkinsonian activity. We have synthesized new substituted quinazolinone derivatives namely 3-Substituted phenyl 2-(3,4-dihydroxyphenyl ethyl amino)-6-substituted quinazolin-4-(3H) ones by incorporating dopamine at 2nd position with the hope to get better antiparkinsonian agents.

MATERIALS AND METHODS

All reagents and solvents were generally used as received from the commercial supplier. Reactions were routinely performed in oven-dried glassware. The melting points of compounds were determined in open capillaries with the help of thermonic melting point apparatus and were uncorrected. Homogeneity of all the newly synthesized compounds was routinely checked by thin layer chromatography (TLC) on silica gel G coated plate of 0.5mm thickness. The eluent was a mixture of different polar and nonpolar solvents in different proportions and spots were visualized under iodine chamber. Elemental analysis (C, H, N) of all the compounds were determined through Perkin-Elmer 2400 elemental analyzer and results were found within ± 0.4% of theoretical values. Infra red (IR) spectra were recorded in KBr on Perkin-Elmer-spectrum RX-I instrument was recorded in cm^{-1}. ^{1}H-NMR spectra were recorded by Bruker DR-X-400 FT-NMR instrument using $CDCl_3$ and $DMSOd_6$.

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General procedure for synthesis of 2-Methyl -6-substituted benzo(1,3) oxazin -4-ones (1a-1b): These compounds were prepared according to the method of bogert and Soil [9]. A mixture of un/substituted anthranilic acids (1.0 mole) and acetic anhydride (100 ml) to the solution of compound 2 in acetic acid (50 ml). The reaction mixture was poured onto crushed ice then left overnight at room temp. The precipitate thus obtained was filtered washed dried and recrystallized with appropriate solvents to obtain compounds 1a-1b.

2-Methyl–benzo(1,3)oxazin-4-one (1a): Yield 90% crystallized from methanol, m.p. 79-8 1°C, Analysis: for $C_9H_7NO_2$, M. Wt. 161.16, Calcd.: C, 67.07; H, 4.38; N, 8.69: Found, C, 67.08; H, 4.34; N, 8.70. IR: 1570, (C=N), 1715, (C=O) and at 1610 (C=C of aromatic ring), ^{1}H-NMR ($CDCl_3$): 2.30 (3H, s, CH_3) and at 6.63-7.75 (4H, m, Ar-H).

2-Methyl-6-bromobenzo(1,3)oxazin-4-one (1b): Yield 83% crystallized from ethanol, m.p. 80 °C, Analysis for $C_9H_6BrNO_2$, M. Wt. 240.05, Calcd. C, 45.03, H, 2.52, N, 5.83, Found, C, 45.06, H, 2.50, N, 5.80. IR: 1577 (C=N), 710 (C=O) and at 1615 (C=C of aromatic ring), 610 (C-Br). ^{1}H-NMR ($CDCl_3$): 2.36 (3H, s, CH_3) and at 6.60-7.65 (3H, m, Ar-H).

General procedure for the synthesis of 3-substituted phenyl-2-methyl-6-substituted quinazolin-4(3H)-ones (2a-2h): To a solution of compound 1a-1b add un/substituted aniline (g, 0.02 mole) was heated on a free flame for 10-20 minutes in a conical flask. After the disappearance of water droplets in a conical flask it was kept at room temperature. On cooling a jelly like mass obtained which was dissolved in ethanol were refluxed and poured in to water. The solid thus obtained was filtered, dried and finally recrystallized appropriate solvent to obtain compounds 2a-2h.

2-Methyl-3-phenyl-quinazolin-4(3H)-one (2a): Yield 76% crystallized from ethanol, m.p. 194 °C, Analysis:for $C_{15}H_{12}N_2O$, M. Wt. 236.27, Calcd.: C, 76.25; H, 5.12; N, 11.86: Found, C, 76.24; H, 5.10; N, 11.87%. IR: 1575 (C=N), 1707 (C=O), 1614 (C=C of aromatic ring) and at 1302 (C-N). ^{1}H-NMR ($CDCl_3$): 2.33 (3H, s, CH_3) and at 6.62-7.65 (9H, m, Ar-H).

3-(2-Chlorophenyl)-2-methylquinazolin-4(3H)-one (2b): Yield 73% crystallized from acetone m.p. 198°C, Analysis: for $C_{15}H_{11}ClN_2O$, M.Wt. 270.71, Calcd.: C, 66.55; H, 4.10; N, 10.35: Found, C, 66.57; H, 4.15; N, 10.30%. IR: 1580 (C=N), 1712 (C=O), 1612 (C=C of aromatic ring), 1307 (C-N) and at 1018 (C-Cl). ^{1}H-NMR ($DMSOd_6$): 2.36 (3H, s, CH_3) and at 6.60-7.65 (8H, m, Ar-H).

3-(2-methoxy Phenyl)-2-methyl Quinazolin-4(3h)-one (2c): Yield 79% crystallized from ethanol m.p. 205 °C, Analysis: for $C_{16}H_{14}N_2O_2$, M.Wt.266.69, Calcd.: C, 72.16, H, 5.30, N, 10.52, Found: C, 72.17, H, 5.32, N, 10.50%. IR: 1573 (C=N), 1715 (C=O), 1616 (C=C of aromatic ring) and at 1304 (C-N). ^{1}H-NMR ($CDCl_3$+$DMSOd_6$): 2.31(3H, s, CH_3), 3.50 (3H, s, OCH_3) and at 6.60-7.65 (8H, m, Ar-H).

3-(4-Methoxy-2-methyl phenyl)-2-methyl quinazolin-4(3H)-one (2d): Yield 75% crystallized from methanol, m.p. 212 °C, Analysis: for $C_{17}H_{16}N_2O_2$, M. Wt. 280.32, Calcd. C, 72.82, H, 5.75, N, 9.99. Found: C, 72.80; H, 5.78; N, 9.95%. IR: 1576, (C=N), 1711, (C=O), 1619, (C=C of aromatic ring) and at 1310 (C-N). ^{1}H-NMR ($CDCl_3$): 2.40 (3H, s, CH_3), 2.10 (3H, s, CH_3), 3.47 (3H, s, OCH_3) and at 6.90-7.70 (7H, m, Ar-H),

3- Phenyl-2-methyl-6-bromo quinazolin-4(3H)-ones (2e): Yield 7% crystallized from Petroleum ether, m.p. 215°C, Analysis: for $C_{15}H_{11}BrN_2O$, M. Wt. 315.16, Calcd. for C, 57.16; H, 3.52; N, 8.89: Found: C, 57.13; H, 3.55; N, 8.83%. IR: 1582 (C=N), 1712, (C=O), 1621 (C=C of aromatic ring), 1315, (C-N) and at 617 (C-Br). ^{1}H-NMR ($DMSOd_6$): 2.46 (3H, s, CH_3), 6.91-7.80 (8H, m, Ar-H).

3-(2-Chloro phenyl)-2-methyl-6-substituted quinazolin-4(3H)-one (2f): Yield 77% crystallized from methanol, m.p. 210 °C, Analysis: for $C_{15}H_{10}BrClN_2O$: M. Wt. 349.61. Calcd. C, 51.53; H, 2.88; N, 8.01: Found: C, 51.50; H, 2.80; N, 8.00%. IR: 1581, (C=N), 1717, (C=O), 1617, (C=C of aromatic ring), 1311, (C-N), 1012, (C-Cl) and at 617 (C-Br). ^{1}H-NMR ($CDCl_3$+$DMSOd_6$): 2.44 (3H, s, CH_3) and at 6.81-7.84 (7H, m, Ar-H).

3-(2-Methoxy phenyl)-2-methyl-6-bromo quinazolin-4(3H)-one (2g): Yield 70% crystallized from ethanol, m.p. 205 °C, Analysis: for $C_{16}H_{13}BrN_2O_2$: M. Wt. 345.19. IR: Calcd. for C, 55.67; H, 3.80; N, 8.12: Found: C, 55.70; H, 3.85; N, 8.13%. 1574 (C=N), 1714 (C=O), 1623 (C=C of aromatic ring), 1312 (C-N), 611 (C-Br) cm^{-1}. ^{1}H NMR ($DMSOd_6$): 2.48 (3H, s, CH_3), 3.48 (3H, s, OCH_3), 6.81-7.84 (7H, m, Ar-H).

3-(4-Methoxy-2-methyl phenyl)-2-methyl-6-bromo quinazolin-4(3H)-one (2h): Yield 70% crystallized from methanol, m.p. 210 °C, Analysis: for $C_{17}H_{15}BrN_2O_2$: M. Wt.

359.22. Calcd. C, 56.84, H, 4.21, N, 7.80: Found: C, 56.80, H, 4.20, N, 7.81%. IR: 1578 (C=N),, 1719 (C=O), 1620 (C=C of aromatic ring), 1317 (C-N) and at 616 (C-Br) cm^{-1}. ^{1}H-NMR ($CDCl_3$): 2.38 (3H, s, CH_3), 2.52 (3H, s, CH_3), 3.46 (3H, s, OCH_3) and at 6.81-7.84 (6H, m, Ar-H).

General procedure for the synthesis of 3-substituted phenyl -2-methylbromo-6-substituted quinazolin-4(3H)-ones 3a-3h: Bromine (g 0.4 mole) in acetic acid was added drop wise to the solution of compound 2a-2h in acetic acid (50 ml). The reaction mixture was poured onto crushed ice then left overnight at room temperature. The precipitate thus obtained was filtrated washed with suitable solvents to furnish compounds. 3a-3h.

3- Phenyl -2-methylbromo quinazolin-4(3H)-one (3a): Yield 78% crystallized from methanol, m.p.221 °C, Analysis: for $C_{15}H_{11}BrN_2O$: M.Wt. 315.16. Calcd. C, 57.16; H, 3.52; N, 8.89: Found: C, 57.10; H, 3.50; N, 8.88%. IR: 1578 (C=N), 1719 (C=O), 1620 (C=C of aromatic ring), 1317 (C-N), 616 (C-Br) cm^{-1}. ^{1}H-NMR ($CDCl_3$+$DMSOd_6$): 3.70 (2H, s, CH_2-Br) and at 6.90-7.70 (9H, m, Ar-H).

3-(2-Chlorophenyl)-2-methylbromo-6-substituted quinazolin-4(3H)-one (3b): Yield 74% crystallized from ethanol, m.p.225 °C, Analysis: for $C_{15}H_{10}BrClN_2O$: Calcd. C, 51.53; H, 2.88; N, 8.01: Found: C, 51.55, H, 2.85, N, 8.06%, M.Wt. 349.61. IR: 1582 (C=N), 1713 (C=O), 1621 (C=C of aromatic ring), 1318 (C-N) and at 1016 (C-Cl) cm^{-1}. ^{1}H NMR ($CDCl_3$): 3.65 (2H, s, CH_2-Br) and at 6.96-7.72 (8H, m, Ar-H).

3-(2-Methoxyphenyl)-2-methylbromo quinazolin-4(3H)-one (3c): Yield 70 crystallized from ethanol, m.p. 228 °C, Analysis: for $C_{16}H_{13}BrN_2O_2$: M.Wt. 345.19. Calcd. C, 55.67; H, 3.80; N, 8.12: Found: C, 55.66; H, 3.82; N, 8.10%, IR: 1574 (C=N), 1719 (C=O), 1615 (C=C of aromatic ring), 1313 (C-N) and at 614 (C-Br) cm^{-1}. ^{1}H NMR ($DMSOd_6$): 3.73 (2H, s, CH_2-Br), 3.50 (3H, s, OCH_3) and at 6.78-7.76 (8H, m, Ar-H).

3-(4-Methoxy-2-methylphenyl)-2-methylbromo quinazolin-4(3H)-one (3d): Yield 73% crystallized from methanol, m.p. 234°C, Analysis: for $C_{17}H_{15}BrN_2O_2$: M.Wt. 359.22. Calcd. C, 56.84; H, 4.21; N, 7.80: Found: C, 56.86; H, 4.20; N, 7.82%, IR: 1585 (C=N), 1718 (C=O), 1620 (C=C of aromatic ring), 1312 (C-N) and at 612 (C-Br) cm^{-1}. ^{1}H NMR ($CDCl_3$+$DMSOd_6$): 2.30 (3H, s, CH_3), 3.49 (3H, s, OCH_3), 3.70 (2H, s, CH_2-Br) and at 6.86-7.89 (7H, m, Ar-H).

3-Phenyl -2-methylbromo-6-bromo quinazolin-4(3H)-one (3e): Yield 70% crystallized from ethanol, m.p. 226 °C, Analysis for $C_{15}H_{10}Br_2N_2O$: M.Wt. 394.06. Calcd: C, 45.72; H, 2.56; N, 7.11: Found: 45.70; H, 2.59; N, 7.10 % IR: 1580 (C=N), 1715 (C=O), 1623 (C=C of aromatic ring), 1308 (C-N) and at 610 (C-Br) cm^{-1}. ^{1}H NMR ($CDCl_3$): 3.65 (2H, s, CH_2-Br), 2.37 (3H, s, CH_3) and at 6.88-7.98 (8H, m, Ar-H).

3-(2-Chloro) phenyl -2-methylbromo-6-bromo quinazolin-4(3H)-one (3f): Yield 75% crystallized from ethanol, m.p. 225°C, Analysis for $C_{15}H_9Br_2ClN_2O$ M.Wt. 428.51. Calcd.: C, 42.04; H, 2.12; N, 6.54: Found: 42.07; H, 2.10; N, 6.56% IR: 1587 (C=N), 1718 (C=O), 1622 (C=C of aromatic ring), 1311(C-N), 612 and at (C-Br) cm^{-1}. ^{1}H-NMR ($CDCl_3$): 3.70 (2H, s, CH_2-Br), 6.98-7.98 (7H, m, Ar-H).

3-(2-Methoxy) phenyl -2-methylbromo-6-bromo quinazolin-4(3H)-one (3g): Yield 71% crystallized from ethanol, m.p. 229 °C, Analysis for $C_{16}H_{12}Br_2N_2O_2$ M.Wt. 429.09: Calcd.: C, 45.31; H, 2.85; N, 6.61: Found: C, 45.30; H, 2.89; N, 6.60%, IR: 1590 (C=N), 1716 (C=O), 1616 (C=C of aromatic ring), 1311 (C-N) and at 613 (C-Br) cm^{-1}. ^{1}H-NMR ($CDCl_3$): 3.46 (3H, s, OCH_3), 3.72 (2H, s, CH_2-Br) and at 6.70-7.86 (7H, m, Ar-H).

3-(4-Methoxy-2-methyl) phenyl -2-methylbromo-6-bromo quinazolin-4(3H)-one (3h): Yield 70% crystallized from ethanol, m.p. 221 °C, Analysis for $C_{17}H_{14}Br_2N_2O_2$, M.Wt. 438.11: Calcd: C, 46.60; H, 3.22; N, 6.39: Found: C, 46.67; H, 3.20; N, 6.40%, IR: 1593 (C=N), 1712 (C=O), 1623(C=C of aromatic ring), 1304 (C-N) and at 611 (C-Br) cm^{-1}. ^{1}H-NMR ($DMSOd_6$): 2.46 (3H, s, CH_3), 3.53 (3H, s, OCH_3), 3.75 (2H, s, CH_2-Br) and at 6.78-7.76 (6H, m, Ar-H).

General procedure for the synthesis of 3-Substituted phenyl 2-(3,4-dihydroxyphenyl ethyl amino)-6-substituted quinazolin-4-(3H) ones (4a-4h): A compound 2a-2h (0.01 mol) and dopamine (0.02 mol) in methanol was refluxed for 10 h the excess of solvent was distilled off and the reaction mixture was poured on to ice. The solid thus obtained was filtered washed with water dried and recrystallized from appropriate solvents to yielded compounds 3a-3h.

3-Phenyl 2-(3, 4-dihydroxyphenyl ethyl amino) quinazolin-4-(3H) one (4a): Yield 78% crystallized from petroleum ether, m.p. 252 °C, Analysis for $C_{23}H_{21}N_3O_3$: M.Wt. 387.43, Calcd.: C, 71.30; H, 5.46; N, 10.85: Found: C, 71.28; H, 5.47; N, 10.80%, IR: 1588 (C=N), 1721 (C=O), 1626 (C=C of aromatic ring), 1312 (C-N) cm^{-1} and at 611 (C-Br). ^{1}H-NMR ($CDCl_3$): 2.40 (4H, d, 2 x CH_2), 3.67 (2H, d, CH_2), 6.87-7.86 (12H, m, Ar-H), 8.80 (1H, s, NH) and at 11.20 (2H, d, 2 x OH).

3-(2-Chlorophenyl)- 2-(3, 4-dihydroxyphenyl ethyl amino) quinazolin-4-(3H) one (4b): Yield 74% crystallized from petroleum ether, m.p. 257 °C, Analysis for $C_{23}H_{20}ClN_3O_3$, M.Wt.421.88, Calcd. for: C, 65.48; H, 4.78; N, 9.96: Found: C, 65.44; H, 4.79; N, 9.93%. IR: 1594 (C=N), 1725 (C=O), 1621(C–C of aromatic ring), 1308 (C-N) and at 1013 (C-Cl) cm^{-1}, ^1H NMR ($CDCl_3$+$DMSOd_6$): 3.45 (4H, d, 2 x CH_2), 3.65 (2H, d, CH_2), 6.76-7.79 (11H, m, Ar-H), 8.82 (1H, s, NH) and at 11.22 (2H, s, 2 x OH).

3-(2-Methoxyphenyl)- 2-(3, 4-dihydroxyphenyl ethyl amino) quinazolin-4-(3H) one (4c): Yield 70% crystallized from acetone, m.p. 255 °C, Analysis for $C_{24}H_{23}N_3O_4$: M.Wt.417.46, Calcd. for C, 69.05; H, 5.55; N, 10.07: Found: C, 69.06; H, 5.57; N, 10.06%. IR: 1576 (C=N), 1729 (C=O), 1623 (C–C of aromatic ring), 1311(C-N) and at 613 (C-Br), cm^{-1}. ^1H NMR ($CDCl_3$): 3.46 (4H, d, 2 x CH_2), 3.70 (2H, d, CH_2), 3.52 (3H, s, OCH_3), 6.79-7.96 (11H, m, Ar-H), 8.70 (1H, s, NH) and at 11.17 (2H, s, 2 x OH).

3-(4-Methoxy-2-methylphenyl)-2-(3,4-dihydroxyphenyl ethyl amino) quinazolin-4-(3H) one (4d): Yield 73% crystallized from methanol, m.p. 261 °C, Analysis for $C_{25}H_{25}N_3O_4$: M.Wt.431.38, Calcd. for C, 69.59; H, 5.84; N, 9.74: Found: C, 69.60; H, 5.82; N, 9.75%. IR: 1589 (C=N), 1730 (C=O), 1622 (C–C of aromatic ring), 1314 (C-N) and at 610 (C-Br) cm^{-1}. ^1H-NMR ($CDCl_3$): 2.24 (3H, s, CH_3), 3.40 (4H, d, 2 x CH_2), 3.55 (3H, s, OCH_3), 2.73 (2H, s, CH_2), 6.83-7.86 (10H, m, Ar-H), 8.84 (1H, s, NH) and at 11.21 (2H, s, 2 x OH).

3-phenyl 2-(3, 4-dihydroxyphenyl ethyl amino)-6-bromo quinazolin-4-(3H) one (4e): Yield 70% crystallized from methanol, m.p. 254 °C, Analysis for $C_{23}H_{20}BrN_3O_3$: M.Wt. 466.33, Calcd. for C, 59.24; H, 4.32; N, 9.01: Found: C, 59.25; H, 4.30; N, 9.00%. IR: 1598 (C=N), 1730 (C=O), 1621(C–C of aromatic ring), 1313 (C-N) and at 615 (C-Br) cm^{-1} ^1H NMR ($DMSOd_6$): 2.44 (4H, d, 2 x CH_2), 3.76 (2H, s, CH_2), 6.79-7.76 (11H, m, Ar-H), 8.85 (1H, s, NH) and at 11.25 (2H, s, 2 x OH).

3-(2-Chloro phenyl)- 2-(3, 4-dihydroxyphenyl ethyl amino)-6-bromo quinazolin-4-(3H) one (4f): Yield 72% crystallized from ethanol, m.p. 260 °C, Analysis for $C_{23}H_{19}BrClN_3O_3$: M.Wt. 500.77. Calcd. for C, 55.16; H, 3.82; N, 8.39: Found: C, 55.14; H, 3.80; N, 8.41% IR: 1590 (C=N), 1733 (C=O), 1620 (C–C of aromatic ring), 1310 (C-N) and at 612 (C-Br) cm^{-1}. ^1H NMR ($CDCl_3$): 3.44 (4H, d, 2 x CH_2), 2.76 (2H, s, CH_2), 6.79-7.76 (10H, m, Ar-H), 8.85 (1H, s, NH) and at 11.25 (2H, s, 2 x OH).

3-(2-Methoxy phenyl)- 2-(3, 4-dihydroxyphenyl ethyl amino)-6-bromo quinazolin-4-(3H) one (4g): Yield 71% crystallized from ethanol, m.p. 253 °C, Analysis for $C_{24}H_{22}BrN_3O_4$. M.Wt. 496.35. Calcd. for: C, 58.07, H, 4.47, N, 8.47, Found: C, 58.09, H, 4.48, N, 8.44% IR: 1590 (C=N), 1710 (C=O), 1626 (C–C of aromatic ring), 1316 (C-N) and at 611(C-Br) cm^{-1}.and ^1H-NMR ($CDCl_3$+$DMSOd_6$): 3.42 (4H, d, 2 x CH_2), 2.66 (2H, s, CH_2), 3.53 (3H, s, OCH_3), 6.79-7.96 (10H, m, Ar-H), 8.75 (1H, s, NH) and at 11.20 (2H, s, 2 x OH).

3-(4-Methoxy-2-methylphenyl)-2-(3,4-dihydroxyphenyl ethyl amino)-6-bromo quinazolin-4-(3H) one (4h): Yield 70% crystallized from methanol, m.p. 263 °C, Analysis for $C_{25}H_{24}BrN_3O_4$. M.Wt. 510.38. Calcd. for: C, 58.83; H, 4.74; N, 8.23: Found: C, 58.80; H, 4.77; N, 8.20 %. IR: 1592 (C=N), 1735 (C=O), 1628 (C–C of aromatic ring), 1309(C-N) and at 614 (C-Br)cm^{-1}.^1H NMR ($DMSOd_6$): 2.52 (3H, s, CH_3), 2.63 (3H, s, CH_2), 3.40 (4H, d, 2 x CH_2), 3.58 (3H, s, OCH_3), 6.78-7.85 (9H, m, Ar-H), 8.77 (1H, s, NH) and at 11.17 (2H, s, 2 x OH).

BIOLOGICAL SCREENING METHOD

All the newly synthesized compounds have been evaluated for their antiparkinsonian activity. The study was carried out on albino rats weighing 100-200g and mice 20-30g of either sex. The animals were feed and allowed water adlibidum. The number of animals in each group was 5. All the compounds were administered in a dose of 100 mg/kg i.p.

Tremor: This activity was done by the method of D.M. Coward and M.S. Dogges [10]. Tremors were induced by oxotremorine (OT) (0.5 mg/kg i.p) in mice 45 min after pretreatment with the test compounds. After 5 min of OT injection, tremors were assessed visually and scored as: 0 = no tremor; 1 = occasional tremor; 2 = intermittent tremors; 3 = continuous tremors. Each animal of a group was scored and tremor index (mean score for each group) determined.

Rigidity: Reserpine (5 mg/kg i.p.) was administered in rats to produce rigidity and after 15 min test compounds were injected. Rigidity was measured 1 h after reserpine administration. To measure rigidity rats were grasped immediately below forelimbs and slight pressure was applied upward against the hind limbs. The degree of resistance was scored according to Goldstein *et al.* [11]: 0 = no resistance; 1= normal resistance; 2 = complete

resistance. A score of 2 was selected as criterion for rigidity and expressed as percentage of animals showing rigidity (score 2) in a group.

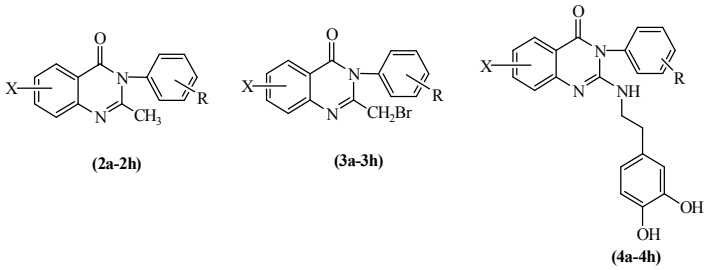
Hypokinesia: This was perform according to the method of Morougo [12]. It was produced by reserpine (5 mg/ kg i.p.) in rats. Locomotor activity was measured after 2h by placing each group of rats in a photoactometer for 15 min and total counts were recorded. The test compounds were administered 15 min after reserpine administration. The percent increase of decrease in counts was calculated on the basis of counts of untreated groups

Acute Toxicity Study: The compounds which showed significant antiparkinsonian activity were investigated for their acute toxicity study in mice (25-30g) of their sex. The compounds were given orally at graded doses to separated group of animals. After 24 h of administration, percent mortality in each group was observed from the data obtained. ALD_{50} values were calculated by the method of Smith [13].

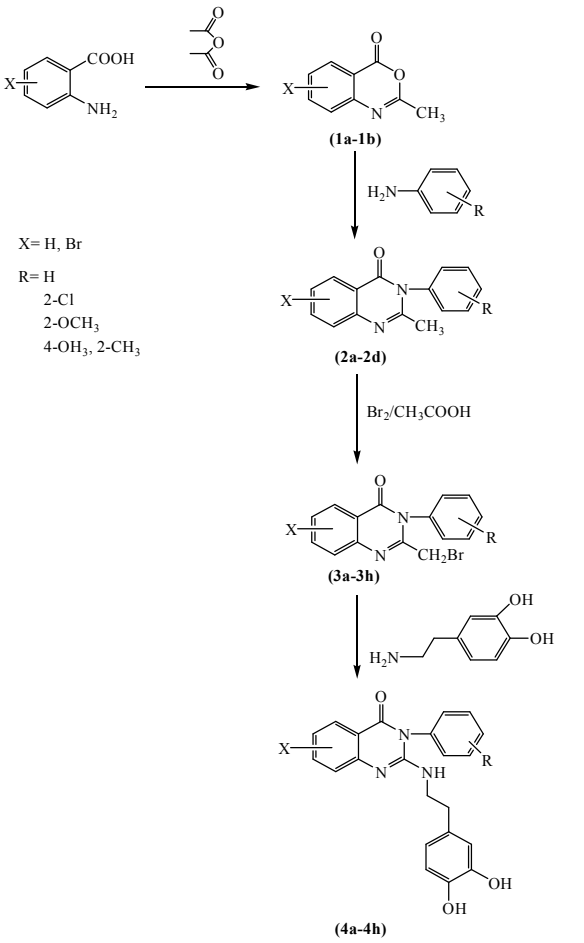
RESULTS AND DISCUSSION

Anti-tremor Activity: Compounds 2a-2h showed moderate anti-tremor activity. The next step compounds i.e, (3a-3h). Compounds 3c, 3f, 3g and 3h showed the good anti-tremor activity. Furthermore, among the compounds 4a-4h. 4b, 4c, 4d, 4g and 4h showed the interesting anti-tremor activity. Moreover compounds 4f (having 2-chloro) showed the most promising anti-tremor activity.

Table 1: Antiparkinsonian activity of compounds 2a-2h, 3a-3h and 4a-4h



Comp. No.	X	R	Oxotremorine induced Tremors in mice (0.5 mg/kg)	Reserpine (5mg/kg) induced Rigidiy (%)	Reserpine (5mg/kg) induced Hypokinesa(% counts)	ALD_{50} mg/kg i.p.
Control	-	-	3.0 ± 0.0	100	14.06	
L-Dopa	-	-	2.60 ± 0.24	80	30.39	
2a.	H	H	2.42 ± 0.29	80	45.2	>1000
2b.	H	2-Cl	2.39 ± 0.24	100	48.7	>1000
2c.	H	4-OCH_3, 2-CH_3	2.35 ± 0.21	70	52.6	>1000
2d	H	2-OCH_3	2.28 ± 0.21	60	55.8	>1000
2e.	Br	H	2.32 ± 0.34	50	49.3	>1000
2f.	Br	2-Cl	2.30 ± 0.31	80	53.1	>1000
2g	Br	4-OCH_3, $2CH_3$	2.40 ± 0.35	40	55.2	>1000
2h.	Br	2-OCH_3	2.38 ± 0.25	50	58.4	>1000
3a.	H	H	2.29 ± 0.30	70	62.85	>1000
3b.	H	2-Cl	2.32 ± 0.25	80	69.9	>1000
3c.	H	4-OCH_3, $2CH_3$	2.25 ± 0.21	40	65.1	>1000
3d.	H	2-OCH_3	2.30 ± 0.43	50	63.5	>1000
3e	Br	H	2.29 ± 0.32	50	61.3	>1000
3f	Br	2-Cl	2.27 ± 0.25	30	55.7	>1000
3g	Br	4-OCH_3, $2CH_3$	2.19 ± 0.15	60	70.45	>1000
3h	Br	2-OCH_3	2.20 ± 0.35	40	68.2	>1000
4a.	H	H	2.29 ± 0.17	60	72.1	>1000
4b	H	2-Cl	2.27 ± 0.15	50	68.3	>1000
4c	H	4-OCH_3, $2CH_3$	2.20 ± 0.28	80	71.7	>1000
4d	H	2-OCH_3	2.22 ± 0.24	30	73.8	>1000
4e	Br	H	2.26 ± 0.24	50	69.4	>1000
4f	Br	2-Cl	2.16 ± 0.25	10	83.7	>1600
4g	Br	4-OCH_3, 2-CH_3	2.21 ± 0.11	20	79.2	>1000
4h	Br	2-OCH_3	2.17 ± 0.29	30	81.3	>1000



Scheme-1: Synthetic route of quinazolinone derivatives

Scheme 1: Synthetic route of quinazolinone dervatives

Rigidity: The compounds 2a, 2f, 3b and 4c were equipotent to L-dopa. While compounds 2e, 2h, 3e, 3d, 4b and 4e showed 50% significant antirigidity activity. The compound 2g, 3c, 3g, 3h and 4d have shown good 60% antirigidity activity. Moreover, compound 3f, 4g and 4h exhibited interesting activity (70-80%). The most promising compound 4f (having 2-chloro) showed anti-rigidity activity.

Anti-hypokinetic Activity: The compound 2a-2h showed the mild anti-hypokinetic activity. the compound 3a, 3c, 3d, 3f, 3g and 3h showed the good anti-hypokinetic activity. The 4a-4h has shown the active compound. Moreover the most promising active compound 4f (3-(2-Chloro phenyl)-2-(3, 4-dihydroxyphenyl ethyl amino)-6-bromo quinazolin-4-(3H)one) have shown interesting anti-hypokinetic activity.

Acute Toxicity: The newly synthesized compounds were also tested for approximate lethal dose ALD_{50} and were found to exhibit a higher value of ALD_{50} i.e. more than 1000mg/kg i.p. except compound 4f which exhibited ALD_{50} of more than 1600 mg/kg i.p. (maximum dose tested) thus indicating the safer nature of the compounds.

CONCLUSION

Antiparkinsonian activity results indicated that all the derivatives of quinazolinones showed antiparkinsonian activity. Moreover, compound 4f (having 2-chlorophenyl ring) showed the highest antiparkinsonian activity which was more effective than standard drug levodopa. Furthermore, compound 4g and 4h also showed interesting antiparkinsonian activity.

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