Antidepressant Activity of Some Novel 1, 2, 4 Triazole Substituted Quinazoline Derivatives

Narendra Joshi[1,*], Anju Goyal[2]

[1]PhD Scholar, [2]Professor & HOD, Dept. of Pharmaceutical Chemistry, BN Institute of Pharmaceutical Education & Research, Udaipur

***Corresponding Author:**
Email: narendrajoshi29@gmail.com

Abstract

Introduction: Quinazoline is an important moiety found natural and used for their biological activity, quinazoline always attract scientist due to its broad therapeutic value. In the present research article we prepared a series of fifteen compound by conjugating to prominent therapeutic active moiety to produce synergistic effect to mimic the antidepressant activity of quinazoline.

Methods: In the process firstly we synthesized substituted 1, 2, 4-triazole and added to the benzoxazine moiety to synthesized derivatives of quinazolines. all the synthesized compound was screened for antidepressant activity by using The Porsolt forced swimming test, The synthesized compounds (20 mg/kg), imipramine (20 mg/kg), and Fluoxetine (20 mg/kg) suspended in aqueous tween 80 (0.5%), were injected as intraperitoneally (i p) and the mouse forced to swim in water cylinder and the vigorous activity observed.

Result: From the synthesized compound Qazo7, Qazo9 and Qazo11 show prominent activity the duration of Immobility is 29.6±0.80, 29.5±1.41 and 29.5±0.62 respectively, compare to standard Fluoxetine and Imipramine.

Conclusion: It can be stated that combination of quinazoline with triazole provide effective antidepressant activity, the synthesized compound may be help to develop potent and safe antidepressant moiety.

Keywords: Quinazoline, Triazole, Antidepressant, Imipramine, Forced swim method

Access this article online

Website:
www.innovativepublication.com

DOI:
10.5958/2394-2797.2016.00023.X

Introduction

In five-membered ring systems the presence of three nitrogen heteroatoms defines an interesting class of compounds, the triazoles. Two well-known methods has been reported for the synthesis of triazole the Pellizzari reaction and the Einhorn–Brunner reaction was discovered in 1911 by *Guido Pellizzari*, and is the organic reaction of an amide and a hydrazide to form a 1,2,4-triazole.[1] The Einhorn–Brunner reaction is the designation for the chemical reaction of imides with alkyl hydrazine to form 1,2,4-triazoles. It was initially described by the German chemist Alfred Einhorn describing N-methylol compounds of amides.[2] Triazole passes many biological activity such as Antibacterial and Antifungal Activity[3], anticonvulsant activity[4], Anticancer activity[5] and antiviral activity[6].

Quinazolinone moiety is an important pharmacophore showing many types of Pharmacological activities. It is also known as a "privileged structure" for drug development. [7] it shows prominent activity as antibacterial[8], antidepressant[9], anticonvulsant[10], and anticancer[11], both the moiety passes effective biological activity, by combining two effective moiety synergistic effect can be achieved for the development of antidepressant compound.

Result and Discussion

In the present study, the synthesis and antidepressant activity of quinazoline derivatives have been described. The synthesis of the substituted 2-methyl-4H-benzo[d][1,3]oxazin-4-one **(2A-2C)** was performed and 4-amino-3-mercapto- 5-substituted-1, 2, 4-triazole **(3a-3e)** were carried out by us using a previous reported method. Synthesis of targeted series was performed by reaction of **2a-2c** with **3a-3e.** All the compound screened for antidepressant activity compound **Qazo7, Qazo9** and **Qazo11** substituted with phenyl, naphthalene and 2-methylaminophenyl show prominent activity the duration of Immobility is **29.6±0.80, 29.5±1.41** and **29.5±0.62** respectively. (**Table 1)** The newly synthesized compounds having substitution of bromine on quinazoline moiety and containing naphthalene, phenyl, 2- methylaminophenyl moiety on triazole were found to have significant *in-vivo* antidepressant activities in the animal models.

The structures of Qazo1–Qazo18 are further supported on the basis of their IR, NMR and mass spectral data. Qazo1 compound show confirmatory peak for the 2991 (CH_3 stretching), 2510 (S-H stretching), presance of peak at near 1300-1100 (C-N stretching) confirm the bonding of quinazoline with triazole susbtitute, absence of peak near about 5.5-5.8 confirm the synthesis of targeted compound. In the mass presnace of parent peak confirm the synthesis.

In conclusion, it can be stated that combination of quinazoline with triazole provide effective antidepressant activity, the synthesized compound may be help to development of potent and safe antidepressant moiety.

Table 1: Antidepressant Activity

S. No	Compound code	Weight of mice	Duration of immobility	Percentage Decrease in immobility duration
				(A-B/A)*100
1	QAzo1	21	54.1±0.26	40.22
2	QAzo2	22	42.4±0.55	53.15
3	QAzo3	21	35.1±0.92	61.22
4	QAzo4	21.5	31.5±1.34	65.19
5	QAzo5	20	45.8±0.72	49.39
6	QAzo6	19	50±0.05	44.75
7	QAzo7	20	29.6±0.80	67.29
8	QAzo8	18	30.5±0.70	66.30
9	QAzo9	20	29.5±1.41	67.40
10	QAzo10	22	30.7±0.98	66.08
11	QAzo11	19	29.5±0.62	67.40
12	QAzo12	20	47.3±0.58	47.73
13	QAzo13	20.5	44±0.49	51.38
14	QAzo14	21	48.7±1.34	46.19
15	QAzo15	22	32.6±0.52	63.98
16	Vehicle	21	90.5±3.3	0.00
17	Imipramine (20mg/kg)	22	24.6±0.9	72.82
18	Fluoxetine (20mg/kg)	19	22.3±0.6	75.36

Experimental section

The melting points were determined by open capillary method and are uncorrected. IR spectra were recorded using KBr on FTIR-8400S Shimadzu. 1H NMR spectra recorded on Joel-FT-NMR-300MHz using DMSO-D_6 as solvent and TMS as internal standard. Mass spectra were recorded on a Jeol (Japan) SX 102/DA-6000 mass spectrometer. All reagents and catalyst were of analytical grade and used directly. All Solvents were distilled before use and dried whenever required. The purity of compound was confirmed by thin layer chromatography using Silica Gel G as the stationary phase on glass plates and suitable mobile phase. Bromination of anthranilic acid was performed by previous reported methods[12].

As per the scheme firstly we synthesized substituted benzoxazine and 4-amino-3-mercapto- 5-substituted-1,2,4-triazole separately from the reported method, then both the substituted moiety reacted to generate the final compound series of substituted2-methyl-3-{3-[susbtituted]-5-sulfanyl-4H-1,2,4-triazol-4-yl}quinazolin-4(3H)-one. The sequence of reaction is drawn in **Scheme I**

Synthesis of potassium dithiocarbazinate[13]

Potassium hydroxide (0.15 mol) was dissolved in absolute ethanol (200 mL). To the above solution, aryl acid hydrazide (0.1 mol) was added and cooled the solution in ice. To this, carbon disulfide (0.15 mol) was added in small portions with constant stirring. The reaction mixture was agitated continuously for a period of 18–23 h. Then, it was diluted with anhydrous ether. The precipitated potassium dithiocarbazinate was collected by filtration. The precipitate was further washed with anhydrous ether (100 mL) and dried under vacuum. The potassium salt thus obtained was in quantitative yield and was used in the next step without further purification.

Synthesis of 4-amino-3-mercapto- 5-substituted-1,2,4-triazole

A suspension of potassium dithiocarbazinate of the respective aromatic esters 2, (0.1 mol) in water (5 mL) and hydrazine hydrate (15 mL, 0.3 mol) was refluxed for 6–7 h with occasional shaking. The color of the reaction mixture changed to green with the evolution of hydrogen sulfide gas (lead acetate paper and odor). A homogenous reaction mixture was obtained during the reaction process. The reaction mixture was cooled to room temperature and diluted with water. On acidification with concentrated hydrochloric acid, the required triazole was precipitated. It was filtered, washed thoroughly with cold water, and recrystallized from ethanol. The completion of the reaction was monitored on TLC by using silica gel-G-coated plates by using ethyl acetate and petroleum ether as the eluent and observed in UV light.

4-Amino-5-[4-(N,N-dimethylamino) phenyl]-3-mercapto- 1,2,4-triazole
Yield: 52%; m. p.: 248^{0}C; IR (KBr) (cm– 1): 3313 (NH stretching), 1608 (C=N stretching); 3131 (aromatic CH stretching), 1314 (C=S stretching), 2978, 2813 (methyl CH stretch), 1232 (N –N=C), 1564, 1542, 1470, 1434 (C=C ring stretching), 1322(C-N stretching);
1H-NMR **δ** (ppm): 13.65 (s, 1H, SH), 6.83, 7.98 (d, 4H, Ar-H), 5.73 (s, 2H, NH_2), 2.99 (s, 6H, N (CH3)2); MS m/z: 235 [M]+.

4-Amino-5-[2-(N-methyl amino) phenyl]-3-mercapto- 1,2,4-triazole Yield: 46%; m.p.: 221^{0}C; IR (KBr) m (cm^{-1}): 3355, 3300 (NH stretching), 1610 (C=N stretching), 3110 (aromatic CH stretching), 1579, 1510, 1467, 1428 (C=C ring stretching), 1319 (C=S stretching), 2940, 2837 (methyl CH stretching), 1286 (N-N=C), 1316 (C-N stretching); 1H-NMR **δ** (ppm): 13.89 (s, 1H, SH), 7.34 (d, 1H of Ar), 7.69 (d, 1H of Ar), 6.63-6.68 (m, 2H of Ar), 5.64 (s, 2H, NH2), 6.18 (q, 1H, NH in NH-CH3), 2.8 (d, 3H,CH3 in NH-CH3); MS m/z: 221 [M]+..

4-Amino-5-(naphthalene-1-yl-methyl)-3-mercapto-1,2,4- triazole Yield: 54%; m.p.: 210^{o}C; IR (KBr) m (cm^{-1}): 3269 (NH stretching), 1625 (C=N stretching), 3162, 3044 (aromatic CH stretching), 1596, 1570, 1495, 1425 (C=C ring stretching), 1315 (C=S stretching), 2929 (methyl CH stretch), 1254 (N–N=C); 1H-NMR **δ** (ppm): 13.48 (s, 1H, SH), 7.32 –8.08 (m, 7H, Ar-H), 5.67 (s, 2H,NH_2), 4.53 (s, 2H, CH_2); MS m/z : 256 [M]+..

4-Amino-5-Phenyl-4H -1,2,4- triazole 3-thiol
Yield: 62 %; m.p.: 206-208^{0}C; IR (KBr) m (cm^{-1}): 3269 (NH stretching), 1625 (C=N stretching), 3162, 3044 (aromatic CH stretching), 1596, 1570, 1495, 1425 (C=C ring stretching), 1315 (C=S stretching), 2929 (methyl CH stretch), 1254 (N–N=C); 1H-NMR d (ppm): 8.6 (s, 1H, SH), 7.4 –8.08 (m, 5H, Ar-H), 5.67 (s, 2H,NH2), MS m/z: 192 [M]+.

4-amino-5-(4-chlorophenyl)-4H-1, 2, 4-triazole-3-thiol
Yield: 43%; m.p.: 248-250^{0}C; IR (KBr) m (cm^{-1}): 3355, 3300 (NH stretching), 1610 (C=N stretching), 3110 (aromatic CH stretching), 1579, 1510, 1467, 1428 (C=C ring stretching), 1319 (C=S stretching), 2940, 2837 (methyl CH stretching), 1286 (N-N=C), 1316 (C-N stretching); 1H-NMR **δ** (ppm): 8.4 (s, 1H, SH), 8.12 (d, 1H of Ar), 7.67 (d, 1H of Ar), 6.63-6.68 (m, 2H of Ar), 5.23 (s, 2H, NH2),; MS m/z: 226 [M]+.

Synthesis of 2-methyl-3-{3-[susbtituted]-5-sulfanyl-4H-1,2,4-triazol-4-yl}quinazolin-4(3H)-one[14]
A mixture of substituted 2-methyl -4H-benzo[d][1,3]oxazin-4-one (20 mmol), 4-Amino-5 Substituted -3-mercapto- 1,2,4-triazole (20 mmol) and glacial acetic acid (40 mL) was refluxed for 6 h. the reaction mixture placed cooled for 24 hours. The reaction mixture was concentrated *in vacuo***,** cooled, poured onto ice water (30 mL) and filtered. The reaction was monitored by TLC using **Chloroform: methanol (2:0.75).** The separated solid was recrystallized from ethanol/ether.

1. **2-methyl-3-{3-[2-(methylamino)phenyl]-5-sulfanyl-4H-1,2,4-triazol-4-yl}quinazolin-4(3H)-one(Qazo1)** Yield, (60.9 %); m. p., 280-282 °C R_f, 0.54. **IR (KBr) m (cm^{-1}):** 2991 (CH_3 stretching), 2510 (S-H stretching), 1319 (C-N stretching)800 (C=C ring stretching) **1H-NMR δ (ppm):** 7.93 (s, 1H, SH), 7.76-7.871 (m, 4H, Ar-H),7.43-7.41 (m, 4H, Ar-H) 4.8 (s, H,NH), 2.8 (s, 3H, NH-CH_3); 2.5 (s, 3H, -CH_3) MS m/z: 350.09 [M]+.
2. **2-methyl-3-(3-phenyl-5-sulfanyl-4*H*-1,2,4-triazol-4-yl)-quinazolin-4(3*H*)-one(Qazo2)** Yield, (54.4%); m. p., 272-274°C R_f, 0.76. **IR (KBr) m (cm^{-1}):** 2987 (CH_3 stretching), 2525 (S-H stretching),744 (C=C ring stretching), **1H-NMR δ (ppm):** 7.8 (s, 1H, SH), 7.53 –7.32 (m, 9H, Ar-H), 2.2 (s, 3H, CH_3); **MS m/z**: 337.10 [M]+.
3. **3-[3-(4-chlorophenyl)-5-sulfanyl-4*H*-1,2,4-triazol-4-yl]-2-methyl-quinazolin-4(3*H*)-one(Qazo3)** Yield, (62.5%); m. p., 280-282°C R_f, 0.55. **IR (KBr) m (cm^{-1}):** 2922 (CH_3 stretching), 850 (C=C ring stretching), 540 (C-Cl Starching) **1H-NMR δ (ppm):** 8.06 (s, 1H, SH), 7.76 –7.33 (m, 7H, Ar-H), 2.1 (s, 3H, CH_3); MS m/z: 371.06 [M]+.
4. **2-methyl-3-[3-(naphthalen-1-ylmethyl)-5-sulfanyl-4*H*-1,2,4-triazol-4-yl]-4a,8a-dihydroquinazolin-4(3*H*)-one(Qazo4)** Yield, (58.0%); m. p., 294-296°C R_f, 0.38. **IR (KBr) m (cm^{-1}):** 2931 (CH_3 stretching), 2858 (CH_2 Streaching) 2530 (S-H stretching), 790(C=C ring stretching), **1H-NMR δ (ppm):** 8.54 (s, 1H, SH), 7.59 –7.08 (m, 11H, Ar-H), 3.9 (s, 2H,-CH_2-), 2.44 (s, 3H, CH_3); MS m/z: 401.13 [M]+.
5. **3-{3-[2-(dimethylamino) phenyl]-5-sulfanyl-4*H*-1,2,4-triazol-4-yl}-2-methylquinazolin-4(3*H*)-one(Qazo5)** Yield, (29.0%); m. p., 286-288°C R_f, 0.69. **IR (KBr) m (cm^{-1}):** 3070 (CH_3 stretching), 2530 (S-H stretching), 781 (C=C ring stretching), **1H-NMR δ (ppm):** 8.22 (s, 1H, SH), 6.55 –7.52 (m, H, Ar-H), 2.88 (s, 6H, $N(CH_3)_2$, 2.42 (s, 3H, CH_3); MS m/z: 380.14 [M]+.
6. **6-bromo-2-methyl-3-{3-[2-(methylamino)phenyl]-5-sulfanyl-4*H*-1,2,4-triazol-4-yl}quinazolin-4(3*H*)-one(Qazo6)** Yield, (36.0%); m. p., 256-258°C R_f, 0.47. **IR (KBr) m (cm^{-1}):** 2900 (CH_3 stretching), 2512 (S-H stretching), 769 (C=C ring stretching), 538 (C-Br Starching) **1H-NMR δ (ppm):** 8.1 (s, 1H, SH), 6.59-7.56 (m, H, Ar-H), 3.8 (s, H,NH), 2.6 (s, 3H, NH-CH_3); 2.4 (s, 3H, -CH_3) MS m/z: 430.00 [M]+.
7. **6-bromo-2-methyl-3-(3-phenyl-5-sulfanyl-4H-1,2,4-triazol-4-yl)-quinazolin-4(3H)-one (Qazo7)** Yield, (46.0%); m. p., 240-242°C R_f, 0.56. **IR**

(KBr) m (cm^{-1}): 2960 (CH_3 stretching), 2357 (S-H stretching), 759 (C=C ring stretching), 667 (C-Br Starching) **1H-NMR δ (ppm):** 8.25 (s, 1H, SH), 7.43 –6.9 (m, 8H, Ar-H), 3.9 (s, H,-CH-), 2.10 (s, 3H, CH_3); MS m/z: 398.98 [M]+.

8. **6-bromo-3-[3-(4-chlorophenyl)-5-sulfanyl-4H-1,2,4-triazol-4-yl]-2-methylquinazolin-4(3H)-one(Qazo8)** Yield, (57.0%); m. p., 274-276°C R_f, 0.46. **IR (KBr) m (cm^{-1}):** 2950 (CH_3 stretching), 2582 (S-H stretching), 752 (C=C ring stretching), 576 (C-Br Starching) **1H-NMR δ (ppm):** 8.23 (s, 1H, SH), 7.40 –6.7 (m, 8H, Ar-H), 3.5 (s, H,-CH-), 1.98 (s, 3H, CH_3)

MS m/z: 434.94 (M^+)

9. **6-bromo-2-methyl-3-[3-(naphthalen-1-ylmethyl)-5-sulfanyl-4*H*-1,2,4-triazol-4-yl]quinazolin-4(3*H*)-one(Qazo9)** Yield, (47.5.0%); m. p., 250-252°C R_f, 0.76. **IR (KBr) m (cm^{-1}):** 2924 (CH_3 stretching), 2560 (S-H stretching), 790 (C=C ring stretching), 500 (C-Br Starching) **1H-NMR δ (ppm):** 8.54 (s, 1H, SH), 8.10 –7.17 (m, 9H, Ar-H), 4.25 (s, 2H,-CH_2-), 1.9 (s, 3H, CH_3); MS m/z: 465.13 [M]+.
10. **6-bromo-3-{3-[2-(dimethylamino)phenyl]-5-sulfanyl-4*H*-1,2,4-triazol-4-yl}-2-methylquinazolin-4(3*H*)-one(Qazo10**) Yield, (37.50%); m. p., 260-262°C R_f, 0.32.**IR (KBr) m (cm^{-1}):** 2955 (CH_3 stretching), 2565 (S-H stretching), 746 (C=C ring stretching), 490 (C-Br Starching)), **1H-NMR δ (ppm):** 8.05 (s, 1H, SH), 6.80 –7.7 (m, H, Ar-H), 2.90(s, 6H, $N(CH_3)_2$, 2.36 (s, 3H, CH_3) MS m/z: 444.02 (M^+)
11. **6,8-dibromo-2-methyl-3-{3-[2-(methylamino)phenyl]-5-sulfanyl-4*H*-1,2,4-triazol-4-yl}quinazolin-4(3*H*)-one(Qazo11)** Yield, (43.00%); m. p., 256-258°C R_f, 0.32 **IR (KBr) m (cm^{-1}):** 3254 (NH- sec. Amine) 2922 (CH_3 stretching), 2566 (S-H stretching), 777 (C=C ring stretching 470 (C-Br Starching) **1H-NMR δ (ppm):** 8.1. (s, 1H, SH), 7.95-7.80 (s, 2H, Ar-H),7.65-6.91 (m, 4H, Ar-H) 3.9 (s, H,NH), 2.6 (s, 3H, NH-CH_3); 2.1 (s, 3H, -CH_3) MS m/z: 507.91 [M]+.
12. **6,8-dibromo-2-methyl-3-(3-phenyl-5-sulfanyl-4*H*-1,2,4-triazol-4-yl)-quinazolin-4(3*H*)-one** Yield, (40.0%); m. p., 254-256°C R_f, 0.45 **IR (KBr) m (cm^{-1}):** 2924 (CH_3 stretching), 2590 (S-H stretching), 790 (C=C ring stretching), 510 (C-Br stretching) **1H-NMR δ (ppm):** 8.67 (s, 1H, SH), 6.25 –7.38 (m, 7H, Ar-H), 3.9-3.7 (s, 2H,-CH-), 2.20 (s, 3H, CH_3); MS m/z: 478.89 (M^+)
13. **6,8-dibromo-2-methyl-3-[3-(naphthalen-1-ylmethyl)-5-sulfanyl-4*H*-1,2,4-triazol-4-yl]-2-methylquinazolin-4(3*H*)-one(Qazo13)** Yield, (32.0%); m. p., 264-266°C R_f, 0.45 **IR (KBr) m (cm^{-1}):** 2980 (CH_3 stretching), 2586 (S-H stretching), 763 (C=C ring stretching), 570 (C-Br Starching) **1H-NMR δ (ppm):** 8.23 (s, 1H, SH), 7.8 –7.42 (m, 6H, Ar-H), 2.58 (s, 3H, CH_3) MS m/z: 512.85 (M^+)
14. **6,8-dibromo-2-methyl-3-[3-(naphthalen-1-ylmethyl)-5-sulfanyl-4*H*-1,2,4-triazol-4-yl]quinazolin-4(3*H*)-one(Qazo14**) Yield, (38.0%); m. p., 288-290°C R_f, 0.74 **IR (KBr) m (cm^{-1}):** 2935 (CH_3 stretching), 2590 (S-H stretching), 780 (C=C ring stretching), 520 (C-Br Starching) **1H-NMR δ (ppm):** 8.40 (s, 1H, SH), 8.05 –7.25 (m, 9H, Ar-H), 4.10 (s, 2H,-CH_2-), 1.9 (s, 3H, CH_3); MS m/z: 542.92 (M^+)
15. **6,8-dibromo-3-{3-[2-(dimethylamino)phenyl]-5-sulfanyl-4*H*-1,2,4-triazol-4-yl}-2-methylquinazolin-4(3*H*)-one(Qazo15)** Yield, (28.0%); m. p., 270-272°C R_f, 0.70. **IR (KBr) m (cm^{-1}):** 2962 (CH_3 stretching), 2500 (S-H stretching), 790 (C=C ring stretching), 572 (C-Br Starching) **1H-NMR δ (ppm):** 7.95 (s, 1H, SH), 6.89 –7.9 (m, 6H, Ar-H), 2.84(s, 6H, $N(CH_3)_2$, 2.45 (s, 3H, CH_3) MS m/z: 521.93 (M^+)

Antidepressant Activity[15]

All the synthesized compounds (Qazo1–Qazo15) were screened for antidepressant activity using The Porsolt forced swimming test[16]. Adult male albino Swiss-Webster (20±2 g) mice were used with free access to food and water. The synthesized compounds (20 mg/kg), imipramine (20 mg/kg), and Fluoxetine (20 mg/kg) suspended in aqueous tween 80 (0.5%), were injected as intraperitoneally (i p) (n= 6). After 1/2 hr, the mouse was dropped into the glass cylindrical container (diameter 10 cm, height 25 cm), containing approximately 20 cm of water at 25 ± 1◦C temperature. Water was replaced between every trial. Each mouse letter for 6 minute at the end of the first 2 min; the animals showing initial vigorous struggling were immobile. The immobility times of each mouse were measured over the period of 4 min. Each mouse was judged immobile when it ceased struggling and remained floating motionless in the water, making only those movements necessary to keep its head above water. Conventional antidepressants decreased the immobility time in this test. Statistical analysis was performed by one-way ANOVA followed by Dunnett's test to evaluate the results. Percentage decrease in immobility duration (%DID) for test and standard drugs was calculated using following formula:

$$\%DID = \frac{A - B}{A} * 100$$

Where A is the duration of immobility (s) in control group and B is the duration of immobility (s) in test group. A comparative bar graph has been produce to show the effect of compound compared to standard compounds. (Fig. 1)

Bar graph of Selective compound compared to control and Standard

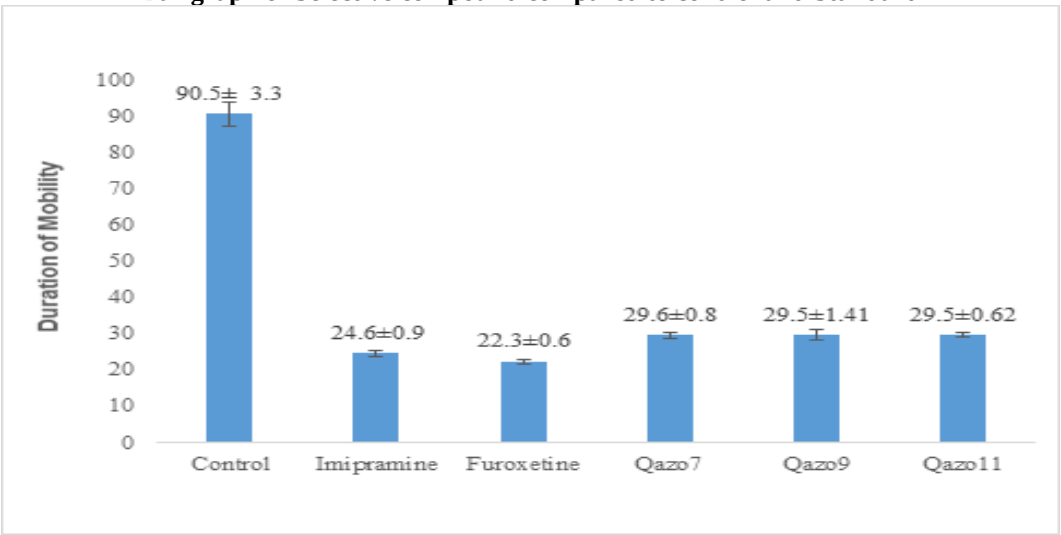
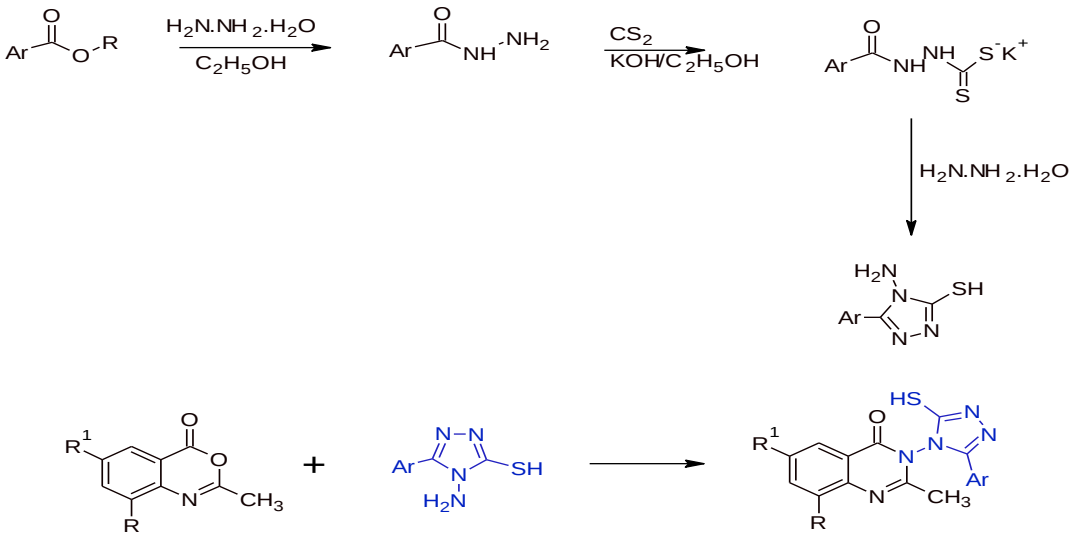


Fig. 1: Effect of treatment with QA3 and QA11 (20 mg/kg, i.p.), imipramine (20 mg/kg, i.p.), and fluoxetine (20 mg/kg, i.p.) on the immobility time in forced swim test. (Values are represented as mean ± S.E.M (n=6). Values are significant at *** p>0.001, compared with control group)

Conflict of interest: No conflict of Interest.



Conflict of interest

No conflict of interest.

References

1. Pellizzari G. *Gazz Chim Ital.* 1911;41:20.
2. Einhorn A. Ueber die N-Methylolverbindungen der Säureamide. *Justus Liebigs Annalen der Chemie.* 1908;361(2-3):113-165.
3. Palekar VS, Damle AJ, Shukla S. Synthesis and antibacterial activity of some novel bis-1, 2, 4-triazolo [3, 4-b]-1, 3, 4-thiadiazoles and bis-4-thiazolidinone derivatives from terephthalic dihydrazide. *European journal of medicinal chemistry.* 2009;44(12):5112-5116.
4. Guo L-J, Wei C-X, Jia J-H, Zhao L-M, Quan Z-S. Design and synthesis of 5-alkoxy-[1, 2, 4] triazolo [4, 3-a] quinoline derivatives with anticonvulsant activity. *European journal of medicinal chemistry*. 2009;44(3):954-958.
5. Wang L-Y, Tseng W-C, Wu T-S, et al. Synthesis and antiproliferative evaluation of 3, 5-disubstituted 1, 2, 4-triazoles containing flurophenyl and trifluoromethanephenyl moieties. *Bioorganic & medicinal chemistry letters.* 2011;21(18):5358-5362.
6. Kumar H, Neena S. Characterization of 1, 2, 4-triazole and their diazotized compound as Bio-active agents. *J Chem & Chem Sci.* 2010;1:1-19.
7. Horton DA, Bourne GT, Smythe ML. The combinatorial synthesis of bicyclic privileged structures or privileged substructures. *Chemical Reviews.* 2003;103(3):893-930.
8. Homer A.B. Nitrofuryl Heterocycles. IV 4-amino-2-(5-nitro-Z-furyl)quinazoline Derivatives *J Am ChemSoc.* 1966;9:408-410.
9. Jatav V, Mishra P, Kashaw S, Stables J. CNS depressant and anticonvulsant activities of some novel 3-[5-

substituted 1, 3, 4-thiadiazole-2-yl]-2-styryl quinazoline-4 (3H)-ones. *European journal of medicinal chemistry.* 2008;43(9):1945-1954.

10. Abdel G. A., Mohammed H. W. Design and synthesis of some new derivatives of 3H-quinazolin-4-one with promising anticonvulsant activity, *Acta Pharm.* 2003;53:127-138.
11. E. Jin Yi et al. Synthesis and antitumor evaluation of novel5-substituted-4-hydroxy-8-nitroquinazolines as EGFR signaling-targeted inhibitors *Bio & Medi Chem.* 2005;13:5613-5622.
12. Webbler A. S., Oates. W. M. The bromination of anthranilic acid. *J Ame Che Soc*. 1990;43:770-773.
13. Sung K, AN-RONG L. Synthesis of [(4, 5-disubstituted-4-H-1, 2, 4-triazol-3-yl) thio] alkanoic acids and their analogues as possible antiinflammatory agents. *Journal of heterocyclic chemistry.* 1992;29(5):1101-1109.
14. Bogert MT, Seil HA. The synthesis of 2-methyl-5-nitro-4-ketodihydroquinazolines from 6-nitroacetanthanil and primary amines. *Journal of the American Chemical Society.* 1905;27(10):1305-1310.
15. Vogel HG. *Drug Discovery and Evaluation: Pharmacological Assays; Including a CD-ROM*: Springer Science & Business Media; 2002:559-560.
16. Porsolt RD, Le Pichon M, Jalfre M. Depression: a new animal model sensitive to antidepressant treatments. *Nature.* 1977;266(5604):730-732.