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Synthesis and Biological Screening of New Derivatives of 2,3-dihydro quinazolin-4(1H)-one and Benzotriazepin- 5(2H)-one for Central Nervous System Activity

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Abstract

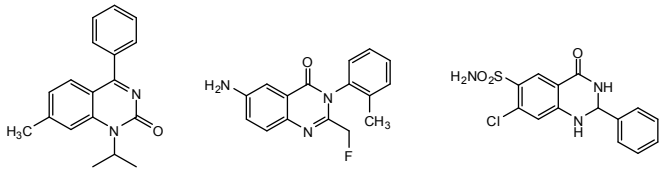
A new syntheses of novel series of 2,3-dihydroquinazolin-4(1H)-one and benzotriazepin- 5(2H)-one derivatives, starting from the same intermediate (II_{a-g}). By varying the substituent on the benzamide moiety of the key intermediate (II_{a-g}) or the conditions of the reactions utilized in this syntheses, the reaction gives rise either quinazolin-4(1H)-one or benzotriazepine-5(2H)-one. The intermediate; 2-methylamino-N-(substituted benzoyl)benzohydrazide (II_{a-g}); was prepared by condensation of N-methyl-isatoic anhydride with different benzoic acid hydrazides. Constructing the intermediates (II_{a-g}) on different cyclo-condensation reactions; either with ethylchloroformate /potassium hydroxide or carbon disulfide/potassium hydroxide, yielded a new series of benzotriazepin-5(2H)-one (III_{a-b}, IV_{a-d}) and a new series of quinazolin4(1H)-one (V_{a-c}, VI_{a-d}). Pharmacological screening of the new benzotriazepinone derivatives revealed that the compounds (VI_{a-b}, IV_{c-d}) exhibited strong CNS depressant activity over clozapine while compounds (VI_a,IV_c) showed the same antipsychotic activity as clozapine with an observed neurotoxicity.

Keywords: Synthesis; Quinazolin-4(1H)-one; Benzotriazepin-5(2H)-one; Anti-psychotic; CNS depressant

Introduction

Quinazolines and their derivatives are associated with diverse pharmacological activities.

Proquazone (1) is clinically used as non-steroidal anti-inflammatory drug [1], Afloqualone (2) has sedative and muscle relaxant effects [2] and Fenquizone (3) is used primarily in the treatment of edema and hypertension [1].



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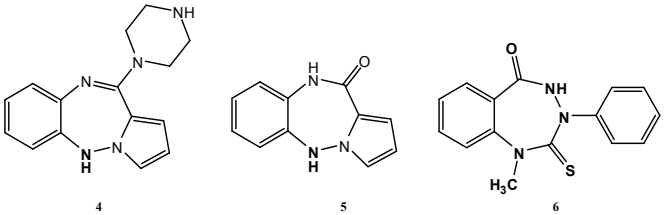
On other hand, Benzotriazepines are mentioned in few literatures in spite of its importance to posses central nervous system [3] and Cholecystokinin (CCK2) antagonist activities [4]. It was reported that compounds (4) and (5) are useful as neuroleptic agents in treatment of schizophrenia [5] and compound (6) found to have the same antipsychotic activity of clozapine [6].



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In view of these observations, the synthesis of some new 1-methyl 2,3-dihydroquinazolin-4(1H)-one and benzo-[e] [1,2,4] triazepin - 5 (2H)-one derivatives was achieved in this work.

Result and discussion

Chemistry

One of the most important classes of nitrogen heterocycles is quinazolinone, benzotriazepinone and its derivatives. These heterocyclic compounds could be obtained from the same pathway depending on the nature of the intermediate and the reaction conditions used [6]. This criteria prompted us to use the benzoyl carbohydrazide derivatives (II_{a-g}) with different substituent on the benzamide moiety as starting intermediate. And varying the carbon source needed for cyclocondensation of the intermediates (II_{a-g}) as well as the reaction conditions. The final heterocyclic compounds produced were confirmed by elemental analysis, IR, ^{1}H NMR, and mass spectroscopy then discussed whatever they are either 2,3-dihydroquinazolin-4(1H)-one or benzotriazepin-5(2H)-one derivatives.

The synthetic pathway to the final compounds is summarized by the following schemes (I,II):-

In scheme I: The reaction of 2-methylamino-N'-(benzoyl) benzo-hydrazide (II_a) with ethyl chloroformate was carried out either in absence or in presence of potassium hydroxide. The amazing results established the two different pathways constructed on this ring closure. At the beginning of this reaction, the resultant compound in absence of KOH was found of melting point differs from that of the compound separated after proceeding the reaction with KOH. The mass spectra proved that compound (III_a) and (IV_a) are of the same molecular weight. On the other hand, applying this reaction with 2-methylamino-N'-(substitutedbenzoyl) benzo- hydrazide (II_{b-h}) intermediates, the final compounds were found to be the same for each intermediate whatever the reaction was carried out in absence or in presence of KOH.

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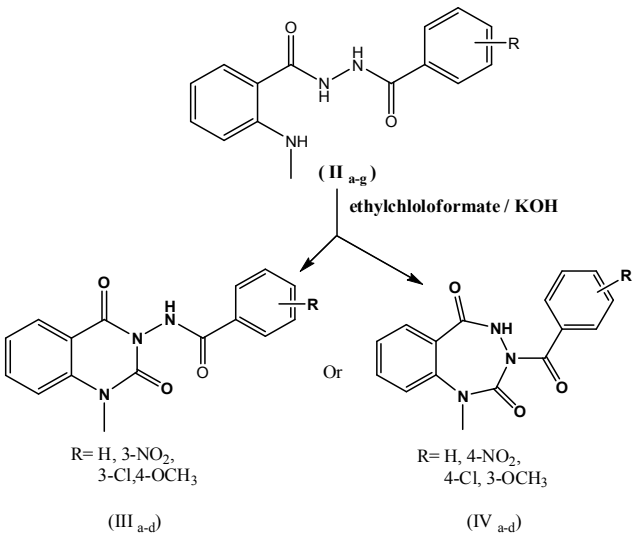


Scheme I: synthetic pathway for compounds III_{a-d} & IV_{a-d}.

The mass spectra were found to be the good tool which differentiate between the two classes (III_{a-d}) and (IV_{a-d}). The mass spectra of (III_a) and (IV_a) were considered the important model to illustrate the difference between quinazlin-2,4(1H,3H)-diones (III_a) and benzotriazepin-2,5(1H,4H)-diones (IV_a), where the possibility of the formation of the neutral fragment 2-methylamino-benzaldehyde (m/z=135) in the seven-member benzo- triazepin-2,5(1H,4H)-diones (IV_a) with intensity more than that in six-membered quinazlin-2,4(1H,3H)-diones (III_a), e.g. the m/z=135(3.0) in (IV_a) and absent in (III_a), the m/z=135(100) in (IV_d-meta-methoxy) and (15.6) in (III_d-para-methoxy), and the m/z=135(1,2) in (IV_b-para-nitro) and (0.6) in (III_b-meta-nitro).

Another parameter is valuable in the mass spectra, the removal of methoxy benzoyl radical (m/z=135) left fragment m/z=191(8.9), stable six-membered neutral molecule, in (III_d) and absent in (IV_d), removal of chlorobenzoyl radical (m/z=139) left fragment m/z=191(0.7) in (III_c) and absent in (IV_c) and removal of nitrobenzoyl radical (m/z=150) left fragment m/z=191(1.9) in (III_b) and (0.6) in (IV_b). From these data, the final compounds (III_{a-d}) and (IV_{a-d}) were confirmed as quinazolin-2,4(1H,3H)-diones and benzotriazepin-2,5(1H,4H)-diones respectively.

In scheme II: It is noticed that the net result of this reaction is greatly affected by the substituent on the benzamide moiety, it's positional and electronic nature, where that of meta-electron withdrawing and that of para-electron donating substituent shifts the reaction towards the quinazolinone-thiones (V_{a-d}) while that of para-electron withdrawing and that of meta-electron donating substituent shifts the reaction towards the benzotriazepinone-thiones (VI_{a-c}). And this may be attributed to the stability of the benzamide nitrogen conjugate base ($N^{2\ominus}$) rather than that of anthranilamide ($N^{1\ominus}$).

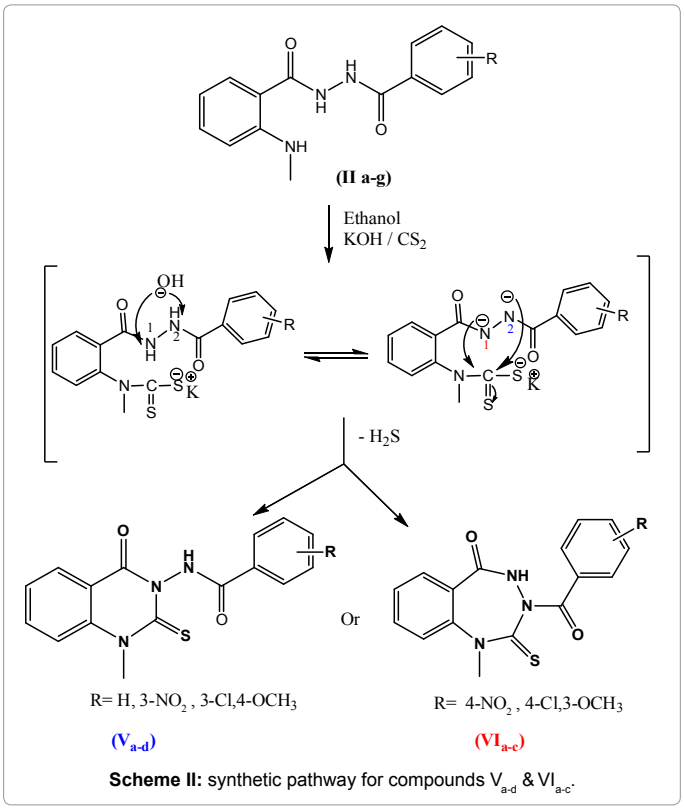
It is noticed, in the ^{1}HNMR spectra of these series, that the NH-singlet peaks of the quinazolinone derivatives (V_{a-d}) appears to be more deshielded than that in the benzotriazepinone derivatives (VI_{a-c}). For example NH-singlet peak of quinazolinone, the 3-chloro-derivative, (V_c) appears at δ=11.7680ppm while that of the benzotriazepinone, the 4-chloro-derivative, (VI_b) which appears at δ=10.6369ppm.

The mass spectra still the differential tool between the quinazoline-thiones (V_{a-d}) and benzotriazepinone-thione (VI_{a-c}), where the fragment stability is proportional to the intensity of fragment existence and this was noticed by the comparison between the mass fragments of the chloro-derivatives (V_c) & (VI_b). It was found after the homolytic fission of the chlorobenzoyl radical (m/z=139) with intensity 100%, the remaining radical (m/z=206) with intensity 15.9% in (V_c) and 7.2% in (VI_b). Removal of $HS^{\ominus}$ (m/z=33) from the target molecule (m/z=345) left a fragment (m/z=312) with intensity 12.1% in (V_c) and 7.5% in (VI_b). Homolytic fission of the chlorobenzoyl radical (m/z=139) from the fragment (m/z=312) left a fragment (m/z=173) with intensity 0.7% in (V_c) and absent in (VI_b). from the previous data, keeping in mind that the six-membered quinazolinone is more stable than the seven-membered benzotriazepinone of the same molecular weight, compound (V_c) is six-membered quinazolinone-thione derivative while (VI_b) is seven-membered benzotriazepinone-thione.

Pharmacology

A newly synthesized group; benzotriazepin-5(2H)-one derivatives (IV_a, VI_{b-c}, IV_{c-d}) were tested for their antipsychotic activities via ptosis test [7] using clozapine as a reference drug. In addition, the CNS depressant activities for such compounds were also examined using forced swim pool test [8]. Also, their neurotoxicity was determined using both rotarod [9] and horizontal screen [10] tests. These compounds (IV_a, VI_{b-c}, IV_{c-d}) were also screened for their anticonvulsant activities against pentylenetetrazole (PTZ)-induced seizures [11].

This is to explore the highly active compound as antipsychotic with least side effects in comparison with reference drug clozapine. It was observed from Table 1 that compounds VI_b, IV_c showed the same antipsychotic activity as the reference drug clozapine whereas they caused complete ptosis in mice at a dose of 3 mg/kg body weight. Moreover, other benzotriazepin-5(2H)-one IV_a, VI_c and IV_d derivatives showed antipsychotic activity but various degree in comparison to that of the reference drug clozapine. The rank of antipsychotic was: clozapine=VI_b=IV_c >IV_d > IV_a=VI_c.



Scheme II: synthetic pathway for compounds V_{a-d} & VI_{a-c}.

The results obtained from Table 2 revealed that, benzotriazepinone (IV_a, VI_{b-c}, IV_{c-d}) exhibited strong CNS depressant activity over reference drug clozapine in mice upon using forced swim test as indicated from their higher immobility times. The rank of CNS depressant activity was IV_d > VI_c > VI_b > IV_a > DMSO > IV_c > clozapine. It was observed that compound IV_d which contain methoxy group at 3-position was cyclized by carbon disulfide/potassium hydroxide showed higher activity than other drugs that contain groups rather than 3-methoxy or cyclized by other methods.

*significantly different from control group at $P < 0.05$ using one way ANOVA followed by Tukeys' Post-hoc test.

In addition, the neurotoxicity for such novel compounds (IV_a, VI_{b-c}, IV_{c-d}) were determined using both rotarod and horizontal screen tests in comparison with the reference drug clozapine (Tables 3 and 4). The rotarod test has demonstrated that compounds IV_a, VI_b, IV_c, and IV_d had similar CNS depressant activity and neurotoxicity similar to clozapine while compound VI_c had slightly weaker activity.

It is observed that Table 4 showed that compounds VI_b and VI_c had strong CNS depressant activity and neurotoxicity as evidenced by the increased percentage of animals that fall from the horizontal screen, while compounds IV_a and IV_d had slightly weaker effect. In addition, all receiving compound IV_c failed to climb to the top of the screen although none of them have fallen of the screen indicating a mild CNS depressant activity and neurotoxicity.

Compound	Ptotic scoring	% effect
Control	0 (no ptosis)	0.0
DMSO	2(1/2 ptosis)	50.0
IV_a	2(1/2 ptosis)	50.0
VI_b	4(complete ptosis)	100.0
IV_c	4(complete ptosis)	100.0
VI_c	2(1/2 ptosis)	50.0
IV_d	3(3/4 ptosis)	75.0
Clozapine	4(complete ptosis)	100.0

Table 1: Evaluation of the antipsychotic activity of compounds and clozapine (3 mg/kg, i.p.) on mice using ptosis test.

Compounds	Immobility time(seconds)
Control	183 ± 5.3
DMSO	160 ± 10.2
IV_a	78 ± 2.9 *
VI_b	71.4 ± 5.4 *
IV_c	80 ± 5.7 *
VI_c	57.8 ± 4.9 *
IV_d	51.8 ± 3.2 *
clozapine	121 ± 6.6 *

Table 2: Evaluation of C.N.S. depressant activity of compounds and clozapine (3 mg/kg, i.p.) on mice using the forced swim test.

Compound	Rotarod toxicity#	% effect
	30 min	
Control	0/5	0
DMSO	1/5	25
IV_a	5/5	100
VI_b	5/5	100
IV_c	5/5	100
VI_c	4/5	80
IV_d	5/5	100
clozapine	5/5	100

Table 3: Evaluation of neurotoxicity of test compounds and clozapine (3 mg/kg, i.p.) using rotarod test in mice.

Compound	A	% Neurotoxicity	B	% Neurotoxicity
Control	0/5	0	0/5	0
DMSO	1/5	20	1/5	20
IV_a	2/5	40	2/5	40
VI_b	3/5	60	0/5	0
IV_c	0/5	0	5/5	100
VI_c	3/5	60	1/5	20
IV_d	2/5	40	0/5	0
clozapine	3/5	60	1/5	20

A = number of mice fall from the screen
B = number of mice that fail to climb the top of the screen

Table 4: Evaluation of neurotoxicity of test compounds and clozapine (3 mg/kg, i.p.) using horizontal screen test in mice.

Compound	A	%	B	%
Control	0/5	0	0/5	0
DMSO	4/5	80	4/5	80
IV_a	4/5	80	4/5	80
VI_b	5/5	100	3/5	60
IV_c	4/5	80	3/5	60
VI_c	4/5	80	3/5	60
IV_d	5/5	100	4/5	80
PTZ	5/5	100	5/5	100

A = number of mice having convulsion within 2 min
B = number of mice dying within 10 min

Table 5: Evaluation of anticonvulsant activity of test compounds and clozapine (3 mg/kg, i.p.) using Pentylenetetrazole (**PTZ**) test in mice.

It was found that compounds IV_a, IV_c and VI_c had mild anticonvulsant activity as evidenced by the reduction in the percentage of animals showing convulsion or death following injection with pentylenetetrazole (Table 5).

Conclusion

Our conclusion herein is the achievement of an excellent synthetic pathway of new series of 2,3-quinazolin-4(1H)-one derivatives and another series of 2,3-dihydro-1H-benzo[e][1,2,4]triazepin-5(2H)-one which was done by different condensation reactions of the benzohydrazides (II_{a-g}) with a carbon source synthone. In the pharmacological screening, It was found that newly synthesized benzotriazepinones revealed that the compounds (IV_a, VI_{b-c}, IV_{c-d}) exhibited strong CNS depressant activity over clozapine while compounds VI_b,IV_c showed the same antipsychotic activity as clozapine with the observed neurotoxicity.

Experimental Protocols

Chemistry

Melting points were determined with a Gallenkamp melting point apparatus (London, UK), and are uncorrected. IR spectra (KBr, cm-1) were recorded on a Bruker Vector, 22FT-IR Spectrometer (Bavaria, Germany). 1HNMR spectra were recorded on Varian Gemini-200 (200 MHz) Spectrometer (CA, USA) using DMSO-d6 as a solvent and tetramethylsilane (TMS) as an internal standard (Chemical shift in d, ppm). Electron impact mass spectra were determined at 70 eV using a GC/MS Shimadzu QP1000EXSpectrometer (Tokyo, Japan). Elemental analyses were determined using Heraeus or Vario EL-III (Elemntar) (Hanau, Germany) or Perkin Elmer Model 2400 (USA) CHN analyzers at the National Research Center and Micro analytical.

Center, Faculty of Science, Cairo University, Egypt. All the results of the elemental analyses were in an acceptable error range. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck),

and spots were visualized by irradiation with ultraviolet light (UV; 254 nm). All chemicals were purchased from Acros Chemicals (Belgium).

General procedure for preparation of 2-methylamino -N'-(substituted-benzoyl) benzo- hydrazide (II_{a-g}) [12]: A mixture of N-methyl isatoic anhydride (8 gm, 0.045 mol) and substituted benzoic acid hydrazide (0.045 mol) in ethanol (50 ml) containing 10 drops glacial acetic acid was heated under reflux for (8-18 hours). The reaction mixture was cooled and the separated solid was filtered and crystallized from ethanol to give the titled compounds.

General procedure for preparation of compounds (III_{a-d}) & (IV_{a-d}): To a solution of 2-methylamino-N'-(substituted benzoyl) benzohydrazide (1 gm, 0.0032 mol) ethylchloroformate (2 ml) was heated under reflux for 2 hours, absolute ethanol (30 ml) was added and the reaction was evaporated to half of its volume, then the mixture was diluted with absolute ethanol (30 ml) and refluxed with KOH (0.24 gm, 0.0037 mol) for 4 hours. The reaction mixture was cooled, acidified with HCl (0.1N), the separated solid filtered and crystallized from appropriate solvent.

N-(1-methyl-2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl) benzamide (III_a)

Yield: 72%; m.p. = 125-127°C crystallized from ethanol. ^{1}HNMR: δ=3.592 (s, 3H, NCH3), 7.360 -8.120 (m, 8H, Ar-), 11.253 (s, 1H, NH, exchangeable) ppm.MS MS m/z (rel.int.)=295.6 (M+1, 1.2), 294.8(M^+, 6.6), 105.2(100), 77.2 (41.9), 76.3(6.2). Analysis for $C_{16}H_{13}N_3O_3$ (295.29): Calcd: C, 65.08; H, 4.44; N, 14.23.Found: C, 65.42; H, 4.69; N, 13.95%.

N-(1-methyl-2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl)-3-nitrobenzamide (III_b)

Yield: 66.6%; m.p. = 292-294°C crystallized from ethanol. ^{1}HNMR: δ = 3.5648(s, 3H, NCH3), 7.3645-8.7707(m, 8H, Ar-H), 11.7711 (s, 1H, NH, exchangeable) ppm. MS m/z (rel.int.) = 340 (M^+, 18.2), 191(0.5), 150 (100), 135(0.6), 134(4.7), 77(12.6), 76(22.2). Analysis for $C_{16}H_{12}N_4O_5$ (340.29): Calcd: C, 56.47; H, 3.55; N, 16.46.Found: C, 56.18; H, 3.33; N, 16.23%.

3-chloro-N-(1-methyl-2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl)benzamide (III_c)

Yield: 62.5 %; m.p. = 271-272°C crystallized from ethanol/dioxan IR: ν = 3408.57(amidic NH-), 3043.12(C-H aromatic), 2992.02(C-H aliphatic) 1724.05 (CO), 1683.55(CO), 1608.34(CO), 1483.96 (C=C). ^{1}HNMR: δ = 3.5568(S, 3H, NCH3), 7.3569-8.0642 (m, 8H, Ar-H), 11.4170(S, 1H, NH, exchan- geable) ppm.MS m/z (rel.int.) = 329 (M^+11.0), 191(0.7), 139 (100), 135 (0.2), 134 (1.2), 77 (10.8), 76(6.6). Analysis for $C_{16}H_{12}ClN_3O_3$ (329.31): Calcd: C, 58.28; H, 3.67; N, 12.74. Found: C, 58.07; H, 3.69; N, 12.79%.

4-methoxy-N-(1-methyl-2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl)benzamide (III_d)

Yield: 64%; m.p. = 125°C crystallized from ethanol ^{1}HNMR δ = 3.549 (S, 3H, NCH3), 3.8206 (S, 3H, OCH3), 7.0606-8.0546 (m, 8H, Ar-H), 11.0710 (s, 1H, NH, exchangeable) ppm. MS m/z (rel.int.) = 326 (M+1, 8.9), 325(M^+, 5.2), 176 (53.1), 150 (52.1), 135 (15.6), 133 (15.6), 120 (100), 77 (48.4), 76 (47.4). Analysis for $C_{17}H_{15}N_3O_4$ (325.32): Calcd: C, 62.76; H, 4.65; N, 12.92.Found: C, 62.53; H, 4.85; N, 13.20%.

3-benzoyl-1-methyl-3,4-dihydro-1H-benzo[e][1,2,4]triazepine-2,5-dione (IV_a)

Yield: 82%; m.p. = 212-214°C crystallized from ethanol. ^{1}HNMR: δ = 3.589 (s, 3H, NCH3), 7.357-8.121(m, 8H, Ar-H), 11.285 (s, 1H, NH, exchangeable) ppm. MS m/z (rel.int.) = 296 (M + 1, 0.8), 295 (M^+, 6.6), 135(3.0),105(100), 77(47.3),76(2.6). Analysis for $C_{16}H_{13}N_3O_3$ (295.29): Calcd: C, 65.08; H, 4.44; N, 14.23.Found: C, 65.14; H, 4.68; N, 14.51%.

1-methyl-3-(4-nitrobenzoyl)-3,4-dihydro-1H-benzo[e][1,2,4] triazepine-2,5-dione (IV_b)

Yield: 83.3%; m.p. = 241-244°C crystallized from ethanol IR: ν = 3417.24 (amidic NH-), 3105.8 (C-H aromatic), 2992.02 (C-H aliphatic) 1687.41, 1606.41, 1517.7 (three C=O), 1481.06 (C=C). ^{1}HNMR δ = 3.5633 (S, 3H, NCH_3), 7.3645-8.4084 (m, 8H, Ar-H), 11.6824 (S, 1H, NH, exchangeable) ppm.MS m/z (rel.int.) = 341 (M^{+1}, 4.3), 340 (M^+, 19.8), 191 (0.6), 150 (100), 135 (1.2), 134 (4.4), 77 (11.8), 76 (18.3). Analysis for $C_{16}H_{12}N_4O_5$ (340.29): Calcd: C, 56.47; H, 3.55; N, 16.46. Found: C, 56.47; H, 3.55; N, 16.46%.

3-(4-chlorobenzoyl)-1-methyl-3,4-dihydro-1H-benzo[e][1,2,4] triazepine-2,5-dione (IV_c)

Yield: 74.1%; m.p. = 150-155°C crystallized from ethanol. IR: ν = 3425.92 (amidic NH-), 3048.91 (C-H aromatic), 2964.05 (C-H aliphatic) 1670.05, 1590.02, 1479.13.7(three C = O), 1317.14 (C = C). ^{1}HNMR δ = 3.5511 (S, 3H, NCH_3), 7.3512 -7.9552 (m, 8H, Ar-H), 11.3634 (s, 1H, NH, exchangeable) ppm.MS m/z (rel.int.) = 329 (M^+, 7.0 139 (100), 135 (0.3), 134 (0.5), 77 (8.3), 76 (6.7). Analysis for $C_{16}H_{12}ClN_3O_3$ (329.31): Calcd: C, 58.28; H, 3.67; N, 12.74. Found: C, 58.13; H, 3.86; N, 12.56%.

3-(3-meyhoxybenzoyl)-1-methyl-3,4-dihydro-1H-benzo[e][1,2,4]triazepine-2,5-dione (IV_d)

Yield: 74.1%; m.p. = 150-155°C crystallized from ethanol. ^{1}HNMR: δ = 3.593 (s, 3H, NCH_3), 3.846 (s, 3H, OCH_3), 7.204-8.124 (m, 8H, Ar-), 11.238 (s, 1H, NH, exchangeable) ppm.MS MS m/z (rel.int) = 326 (M^{+1}, 4.1), 176 (11.6), 149.7 (12.2), 135 (100), 134 (49.4), 119.8 (22.1), 77 (30.2), 76 (19.8). Analysis for $C_{17}H_{15}N_3O_4$ (325.32): Calcd: C, 62.76; H, 4.65; N, 12.92. Found: C, 62.63; H, 4.59; N, 13.12%.

General procedure for preparation of compounds (V_{a-d}) & (VI_{a-c}): To a solution of 2-methylamino-N-(substituted benzoyl) benzohydrazide (1 gm, 0.0032 mol) and potassium hydroxide (0.24 gm, 0.0032 mol) in ethanol 95% (20 ml), carbon disulfide (0.115 gm.0.0032 mol) was added. The reaction mixture was stirred on cold for 2 hours then heated under reflux for 8 hours, concentrated to half volume and then poured into cold water (100 ml). The separated solid was filtered, dried and crystallized from appropriate solvent to give the titled compounds.

N-(1-methyl-4-oxo-2-thioxo-1,2-dihydroquinazolin-3(4H)-yl) benzamide (V_a)

Yield: 60%; m.p. = 184-186°C; crystallized from ethanol ^{1}HNMR: δ = 4.1227 (s, 3H, NCH3), 7.4853-7.9591(m, 9H, Ar-H), 11.7099 (s, 1H, NH, exchangeable) ppm.MS *m/z* (rel.int.)=311 ($M^{+\cdot}$ 14.7), 278 (5.2), 206 (3.2), 135 (0.9), 134 (2.9), 105 (100), 77 (46.7), 76 (10.1). Analysis for $C_{16}H_{13}N_3O_2S$ (311.6): Calcd: C, 61.72; H, 4.21; N, 13.50.Found: C, 61.28; H, 4.38; N, 13.82%.

N-(1-methyl-4-oxo-2-thioxo-1,2-dihydroquinazolin-3(4H)-yl)-3-nitrobenzamide (V_b)

Yield: 65 %; m.p = 190-193°C; crystallized from ethanol MS-analysis:m/z(rel.intensity) = 358 (M^+2, 1.4), 357 (M^{+1},0.3), 356 (M^+,13.8), 323 (7.1), 206 (9.1), 135 (92.9), 134 (100),77 (47.8),76 (38.5). Analysis for $C_{16}H_{12}N_4O_4S$ (356.36): Calcd: C, 53.93; H, 3.39; N, 15.72. Found: C, 54.03; H, 3.50; N, 15.60%.

3-chloro-N-(1-methyl-4-oxo-2-thioxo-1,2-dihydroquinazolin-3(4H)-yl) benzamide (V_c)

Yield: 63.6%; m.p. = 237°C crystallized from ethanol / dioxan ^{1}HNMR: δ = 4.1211 (s, 3H, NCH_3), 7.4868-8.1272 (m, 8H, Ar-H), 11.7680 (s, 1H, NH, exchangeable) ppm. MS-analysis: m/z (rel.int.) = 346 (M^{+1}, 4.5), 345(M^+, 17.7), 312 (12.1), 206 (15.9), 139 (100), 135 (2.1), 134 (4.6), 77 (21.3), 76 (15.5). Analysis for $C_{16}H_{12}ClN_3O_2S$ (345.8): Calcd: C, 55.57; H, 3.50;N, 12.15. Found: C, 55.80; H, 3.58; N, 12.27%.

4-methoxy-N-(1-methyl-4-oxo-2-thioxo-1,2-dihydroquinazolin-3(4H)-yl) benzamide (V_d)

Yield: 57.47.6%; m.p. = 151-152°C crystallized from ethanol. ^{1}HNMR: δ = (s, 3.8326, 3H, OCH3), 4.1215 (s, 2H, NCH_3), 7.0568-8.3518 (m, 8H, Ar-H), 11.3959 (s, 1H, NH, exchangeable) ppm. MS-analysis: m/z (rel.int.) = 341 (M^+, 14.9), 308 (5.0), 206 (3.3), 135 (100), 134 (12, 7), 77 (34.5), 76 (9.4). Analysis for $C_{17}H_{15}N_3O_3S$ (341.38): Calcd: C, 59.81; H, 4.43; N, 12.31. Found: C, 59.52; H, 4.57; N, 12.65%.

1-methyl-3-(4-nitrobenzoyl)-2-thioxo-3,4-dihydro-1H-benzo[e][1,2,4]triazepin-5(2H)-one VI_a

Yield: 70%; m.p. = 160°C crystallized from ethanol. ^{1}HNMR (200MHz): δ = 4.1227 (s, 3H, N-CH_3), 7.3605-8.4258 (m, 8H, Ar-H), 11.7135 (s, 1H, NH, exchangeable) ppm. MS m/z (rel.int) = 346(M^+1, 3.6), 345 (M^+, 15.2), 312 (7.5), 206 (7.2), 139 (100), 135 (4.1), 134 (9.2), 77 (19.5), 76 (13). Analysis for $C_{16}H_{12}N_4O_4S$ (356.36): Calcd: C, 53.93; H, 3.39;N, 15.72.Found: C, 53.62; H, 3.57; N, 15.91%.

3-(4-chlorobenzoyl)-1-methyl-2-thioxo-3,4-dihydro-1H-benzo[e][1,2,4]triazepin-5(2H)-one VI_b

Yield: 57.14%; m.p. = 237°C crystallized from ethanol / dioxan ^{1}HNMR: d = 4.1227 (s, 3H, NCH3), 6.5682-7.9591(m, 8H, Ar-H), 10.6369 (s, 1H, NH, exchangeable) ppm. MS m/z (rel.int) = 345 (M^+, 15.2), 312 (7.5), 206 (7.2), 139 (100), 135 (4.1), 134 (9.2), 77 (19.5), 76 (13). Analysis for $C_{16}H_{12}ClN_3O_2S$ (345.8): Calcd: C, 55.57; H, 3.50;N, 12.15.Found: C, 55.85; H, 3.81; N, 11.96%.

3-(3-methoxybenzoyl)-1-methyl-2-thioxo-3,4-dihydro-1H-benzo[e][1,2,4]triazepin-5(2H)-oneVI_C

Yield: 57.5 %; m.p. = 211-213°C crystallized from ethanol. ^{1}HNMR: δ = 4.159 (s, 3H, NCH_3), 3.843 (s, 3H, OCH_3), 7.203-8.171(m, 8H, Ar-H), 11.584 (s, 1H, NH, exchangeable) ppm. MS-analysis: m/z (rel. intensity) = 341 (M^+, 8.9), 308 (2.6), 206 (0.3), 135 (100), 134 (11.2), 77 (19.9), 76 (5.0). Analysis for $C_{17}H_{15}N_3O_3S$ (341.38): Calcd: C, 59.81; H, 4.43; N, 12.31. Found: C, 60.07; H, 4.38; N, 12.37%.

Pharmacology

Animals: Male albino rats and male mice, weighing 150– 200 g and 20–25 g each, respectively, were used. All experimental animals were provided from Faculty of Veterinary Medicine, Zagazig University, Egypt. All animals were held under standard laboratory conditions in the animal house (temperature 27°C) with 12/12 light-dark cycle. They were fed laboratory diet and water ad libitum. All experiments were carried out using 5 animals per group. The animal experiments were performed in accordance with international guidelines.

Antipsychotic activity evaluation using Ptosis test: It was carried out according to the method described by [7]**.** Mice were divided into 7 equal groups (n=5). The first group was labelled as control and injected i.p. with the solvent (DMSO) while the second group was injected (i.p.) with clozapine at a dose of 3 mg/kg. The tested compounds (IV_a,VI_{b-c}, IV_{c-d}) were injected (i.p.) to the other groups at a dose of 3 mg/kg. Every mouse was observed for the presence or absence of complete ptosis. The ptosis was rated as the fraction of the eyelid closure from normal. The ptosis ratio was made 4 for complete ptosis, 3 for 3/4, 2 for 1/2, and 1 for 1/4 ptosis.

CNS depressant activity evaluation using Forced swim pool test: The forced swim pool method (FSP) described by [8] was followed. Mice were classified into 7 groups, each of five (n=5). And then injected i.p. with solvent (control), reference drug clozapine, and test compounds (IV_a, VI_{b-c}, IV_{c-d}) at a dose of 3 mg/kg body weight 30 min before the test session. The animals were placed in a chamber (diameter: 45 cm, height: 20 cm) containing water up to height of 15 cm at 25 ± 2 °C. The period of immobility (passive floating without struggling and making only those movements which are necessary to keep its head above the surface of water) during the 5 min test period was measured and recorded.

Neurotoxicity screening

Rotarod test: Minimal motor impairment was measured in mice by the rotarod test [9]**.** The mice were trained to stay on an accelerating rotarod that rotates at 4–10 rpm. The rod diameter was 3.2 cm. Trained mice were classified into 7 groups, each of five (n=5) and then injected i.p. with DMSO (control), clozapine, and test compounds (IV_a, VI_{b-c}, IV_{c-d}) at a dose of 3 mg/kg body weight. Neurotoxicity was determined 30 min post treatment as the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of three trials.

Horizontal screen test: Neural impairment was also determined by failure of mice to perform successfully the horizontal screen test [10]**.** The apparatus consisted of a 13 9 14 cm^2 wire screens which was mounted horizontally on a steel rod. The rod was supported at both ends and could be inverted through an arc of 180°. Trained mice were classified into 7 groups, each of five and then injected i.p. with DMSO (control), clozapine, and test compounds (IV_a,VI_{b-c}, IV_{c-d}) at a dose of 3 mg/kg body weight. The animals were placed individually on the top of the screen and the rod was then rotated (mice unable to climb to an upright position within 1 min were rated as failures 30 min after drugs administration, two values were recorded: (A) The number of mice that fall from the screen and (B) The number of mice that fail to climb the top of the screen (i.e., the sum of those that remain clinging to the bottom of the screens and those that falls from the screen). Mice were divided into 7 equal groups (n=5). The first group was injected i.p. with DMSO (control) while clozapine and tested compounds were injected (i.p.) to the other groups at the same dose level.

Anticonvulsant activity

The anticonvulsant activities of the compounds (IV_a, VI_{b-c}, IV_{c-d}) were determined against pentylenetetrazole-induced seizures [11]**.** One hour later, mice were injected with pentylenetetrazole 70 mg/kg subcutaneously in scruff of neck. After 1-2 min of PTZ injection, the animals develop sequence of excitement, myoclonic jerks, clonic seizures, one or more maximal tonic seizures and finally death. Seizure latency was defined as the time elapsed from injection of PTZ to the first two the myoclonic jerks of the forelimbs. This has been considered to be the first sign of the beginning of seizure activity [13]**.** Animals devoid of generalized convulsions were considered to be protected and their results were represented as protection percentage.

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