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SYNTHESIS OF NEW 1,2,4-TRIAZOLOQUINAZOLINE DERIVATIVES AS CNS MODULATORS

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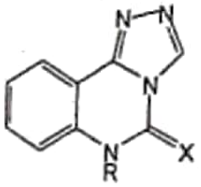
ABSTRACT

A series of 1,2,4-triazolo[4,3-c]quinazoline-3-thiol was synthesized by reacting isatoic anhydrides (I_a,I_b) with thiosemicarbazide to yield the appropriate 2-acylhydrazinocarbothioamides (II_a,II_b) which were cyclized to afford 5-(2-substituted aminophenyl)-1,2,4-triazol-3-thiols (III_a,III_b) using sodium hydroxide. The triazol derivatives (III_a,III_b) were cyclized to the new 1,2,4-triazolo[4,3-c]quinazoline-3-thiol (IV) upon condensation with aromatic aldehydes. Whereas, cyclization of (III_a,III_b) with formaldehyde unexpectedly afforded 3-hydroxymethyl-1,2,4-triazolo[1,5-c]quinazolin-2-thione (VI_a, VI_b). The last reaction is the role-play to the formation of a series of 1,2,4-triazolo[1,5-c]quinazoline-2-thiol (VI_c, VI_d, VII) upon boiling of the appropriate 1,2,4-triazolo[4,3-c]quinazoline-3-thiol in ethanol with acidified formaldehyde. Also, alkylation of 3-thiol derivatives (IV) with the appropriate alkyl halide in alkaline medium afforded a new series of 3-alkyl (or 3-aralkyl) thio-1,2,4-triazolo[4,3-c]quinazolines (V_{a-h}). Otherwise, alkylation of 5-(2-methylaminophenyl)-1,2,4-triazol-3-thiol (III_a) was affected firstly and followed by condensation with either carbon disulfide or hydroxybenzaldehyde to produce 3-alkylthio-6-methyl-1,2,4-triazolo[4,3-c]quinazolin-5(6H)-thione (IX) or 3-alkylthio-5-(hydroxyphenyl)-6-methyl-1,2,4-triazolo[4,3-c]quinazoline (V_{i-l}) respectively. Oxo-desulfuration was the key-procedure for preparation of 3-hydroxy-6-methyl-5-(4-nitrophenyl)-1,2,4-triazolo[4,3-c]quinazoline (X) from its thione analogue. The new triazoloquinazoline derivatives were subjected to preliminary pharmacological screening, where compounds (VI_f, V_b, VI_a, VI_b, VI_d, X) produced a moderate to high CNS stimulant effect when tested on mice. Furthermore, compound (VI_a) was tested by recording the electroencephalographic changes induced by its intravenous injection in conscious rabbits which gave noticeable results.

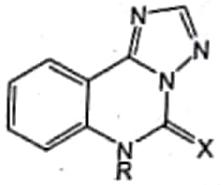
INTRODUCTION

During the last two decades c-annellated 1,2,4-triazoloquinazolines have gained great attention as reactive CNS modulators acting as benzodiazepine receptor ligands[1-5] and adenosine antagonists[6-10].

Both isomers triazolo[4,3-c]quinazoline (1) and triazolo[1,5-c]quinazoline (2) were found to be active.



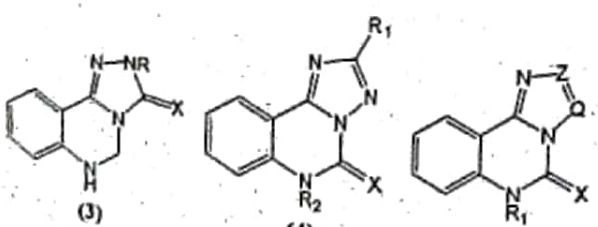
Triazolo[4,3-c]quinazoline
(1)



Triazolo[1,5-c]quinazoline
(2)

So far no exact structure-activity relationship for such ring system has been presented. However, the following structural features were found to retain CNS activity and thus were used as a base for our design for new compounds.

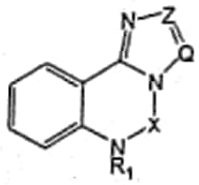
Chen and Hutchison[1,2] showed that aromaticity of the quinazoline ring is not a necessity for activity when they synthesized 5,6-dihydro[1,2,4]triazolo[4,3-c]quinazoline-3-one and 3-thione (3) and found to be active as BZR ligands. Alkylation at 6-position retain the same activity as shown in series (4)[3,4] in which R_2=alkyl, hydroxyalkyl or aralkyl. The triazol ring has two sites for substitution 2 and 3, Z and Q in formula (5), as shown by many workers, where, Q ≠ Z = N or CR (where, R may be aromatic or aliphatic substitution or it may be H). All showed CNS activity.



(3) (4) (5)

X = O or S and R = alkyl

The previous findings prompted us to synthesize some novel 1,2,4-triazolo[4,3-c]quinazolines and 1,2,4-triazolo[1,5-c]quinazolines having the following structures:



Where,
R_1= CH_3 or m-trifluorophenyl
X = CS, CH_2 or (CH-substituted phenyl)
Q ≠ Z = NR_2 (where R_2= H or hydroxymethyl) or CY (where Y= thio, alkylthio or oxo group)
The newly synthesized compounds were evaluated for their CNS activity.

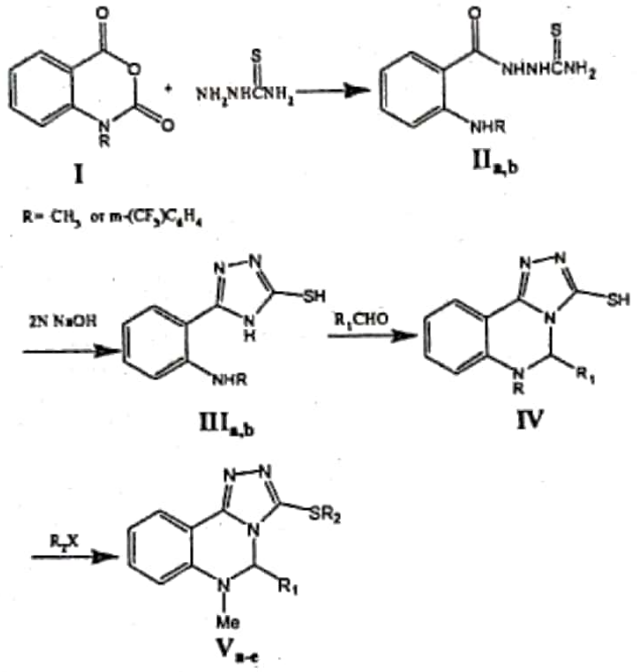
DISCUSSION

The novel triazoloquinazoline targets were designed and prepared as shown in the following schemes (I-III).

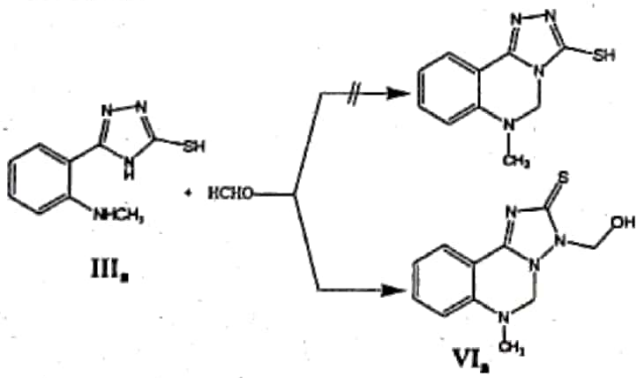
Reaction of thiosemicarbazide with N-methylisatoic anhydride (I_a) or N-(3-trifluoromethylphenyl)isatoic anhydride (I_b) in glacial acetic acid at room temperature afforded the novel 2-(2-(methylamino)benzoyl) hydrazinecarbothioamide (II_a) and 2-(2-(3-trifluoromethylphenyl)aminobenzoyl) hydrazinecarbothioamide (II_b) respectively. The appropriate 2-acylhydrazinecarbothioamide (II_a) or (II_b) was refluxed with 2N sodium hydroxide solution followed by neutralization to obtain the novel 5-(2-methylaminophenyl)-1,2,4-triazol-3-thiol (III_a) and 5-(2-(3-trifluoro-methylphenyl)aminophenyl)-1,2,4-triazol-3-thiol (III_b) respectively. The novel targets; 1,2,4-triazolo[4,3-c]quinazoline-3-thiols (IV) were prepared by condensation of the corresponding

intermediate (III_a) or (III_b) with different aromatic aldehydes by refluxing in glacial acetic acid. Thioethers (V) were produced in a fairly good yield by steering thiol compounds (IV_{a-e}) with alkyl halide in aqueous sodium hydroxide at room temperature.

Scheme I:

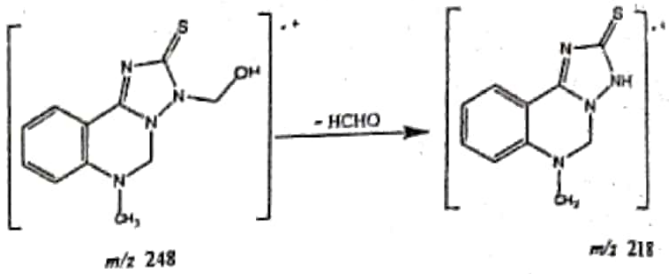


Application of internal Mannich reaction on the diamine intermediate; 5-(2-methylaminophenyl)-1,2,4-triazol-3-thiol (III_a); with formaldehyde, the designed product, 6-substituted-5,6-dihydro-1,2,4-triazolo[4,3-c]quinazoline-3-thiol was not formed. Instead, the unexpected product, 3-hydroxymethyl-6-methyl-5,6-dihydro-1,2,4-triazolo[1,5-c]quinazolin-2-thione (VI_a) was formed.



The structure of the synthesized compounds was identified by ^{1}H-NMR spectra, for example, the spectrum of VI_a showed the characteristic methylene singlet at δ 5.0 ppm for N-C<u>H</u>$_2$-N and a doublet for N-C<u>H</u>$_2$-OH at δ 5.4 ppm which is split by coupling with the adjacent hydroxylic proton which in turn showed a signal in the aromatic region overlapping with the aromatic protons.

Moreover, the mass spectrum of such ring system was characterized by its fragmentation pattern. Where, 3-hydroxymethyl-6-methyl-5,6-dihydro-1,2,4-triazolo-[1,5-c]quinazolin-2-thione (VI_a) showed a molecular ion peak at m/z 248 corresponding to $C_{11}H_{12}N_4OS$ of VI_a and a base peak at m/z 218 indicating a loss of CH_2O moiety and giving the more stable compound without the hydroxymethyl group as shown below.



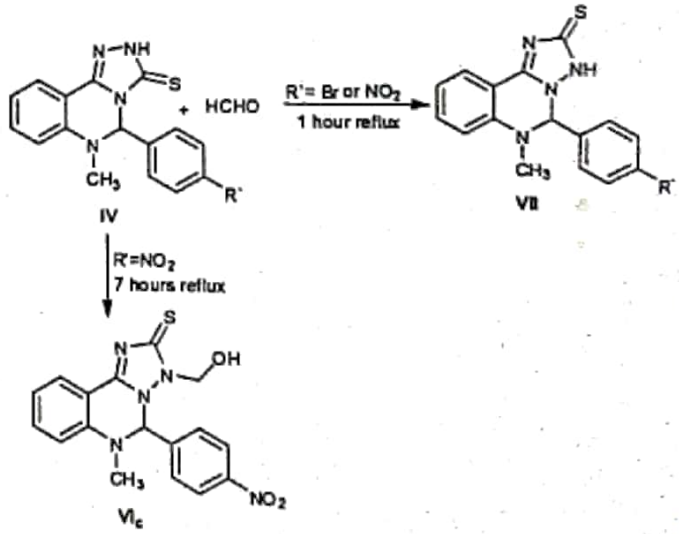
Also, IR spectrum of the same compound showed the characteristic hydroxyl stretching vibration band at 3304 cm^{-1}.

Isomerization of 1,2,4-triazolo[4,3-c]quinazoline to 1,2,4-triazolo[1,5-c]quinazoline has been known for decades[11,12]. Certain reaction conditions enhance this kind of isomerization. The mechanism of this rearrangement is not known exactly.

In the present work, the isomerization was found to occur by refluxing the 1,2,4-triazolo[4,3-c]quinazoline isomer with formaldehyde in ethanol in presence of acetic acid.

The reaction between 1,2,4-triazol[4,3-c]quinazoline (IV_{a-c}) and formaldehyde was originally carried out in an attempt to synthesize hydroxymethyl derivatives of 5-aryl substituted triazoloquinazoline (Scheme II).

Scheme II:



Unexpectedly, the product was found to differ according to the type of the 5-aryl substituent and also the time of reflux. Where, refluxing 6-methyl-5-(substitutedphenyl)-5,6-dihydro-1,2,4-triazolo[4,3-c]quinazoline-3-thione (IV) with formaldehyde for 1 hour gave the corresponding 6-methyl-5-(substitutedphenyl)-5,6-dihydro-1,2,4-triazolo[1,5-c]quinazoline-2-thione (VII) isomer when the 5-substituent was p-nitrophenyl or p-bromophenyl. However, refluxing 6-methyl-5-(4-nitrophenyl)-5,6-dihydro-1,2,4-triazolo[4,3-c]quinazoline-3-thione (IV_a) with formaldehyde for 7 hours gave 3-hydroxymethyl-6-methyl-5-(4-nitrophenyl)-5,6-dihydro-1,2,4-triazolo[1,5-c]quinazolin-2-thione (VI_c).

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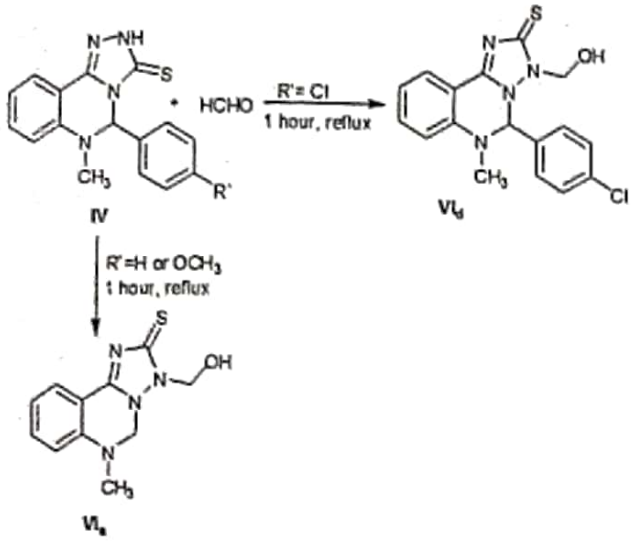
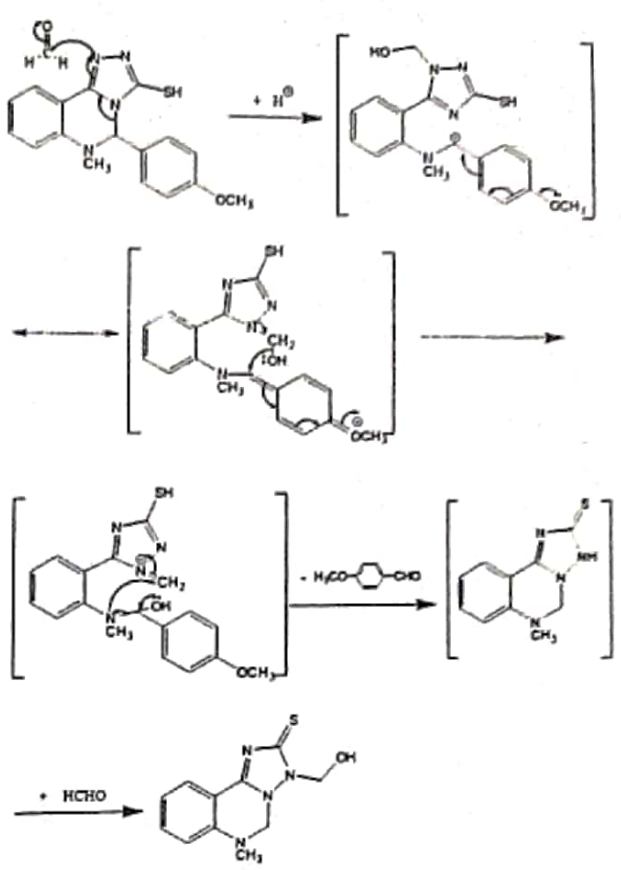


When the 5-substituent was p-chlorophenyl the product was 5-(4-chlorophenyl)-3-hydroxymethyl-6-methyl-5,6-dihydro-1,2,4-triazolo[1,5-c]quinazolin-2-thione (**VI$_d$**), but when the 5-substituent was phenyl or p-methoxyphenyl unexpectedly the product was 3-Hydroxymethyl-6-methyl-5,6-dihydro-1,2,4-triazolo[1,5-c]quinazolin-2-thione (**VI$_a$**) which confirmed the same compound in Scheme 1.

The structures of the synthesized compounds were identified by their spectral analysis. Where ^{1}H-NMR spectrum of 6-methyl-5-(4-nitrophenyl)-5,6-dihydro-1,2,4-triazolo[1,5-c]quinazoline-2-thiol (**VII$_a$**) showed a singlet at δ 6.5 ppm for the C_5 proton with absence of the peaks of hydroxymethyl group. IR spectra of both **VIII$_a$** and **VIII$_b$** showed the characteristic secondary NH stretching vibration band at 3400 cm^{-1}. Moreover, the mass spectra gave molecular ion peak at (*m/z* 339) corresponding to $C_{16}H_{13}N_5O_2S$ of **VII$_a$** and molecular ion peak (*m/z*, M +2) at 374 corresponding to $C_{16}H_{13}BrN_4S$ of **VII$_b$**.

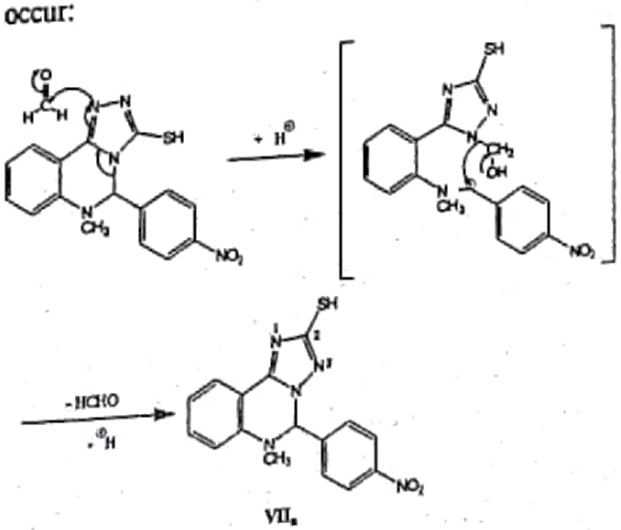
Both 3-hydroxymethyl-6-methyl-5-(4-nitrophenyl)-5,6-dihydro-1,2,4-triazolo[1,5-c]-quinazolin-2-thione (**VI$_c$**) and 5-(4-chlorophenyl)-3-hydroxymethyl-6-methyl-5,6-dihydro-1,2,4-triazolo[1,5-c]quinazolin-2-thione (**VI$_d$**) were characterized by their ^{1}H-NMR spectra which showed in addition to the benzylic proton singlet at δ 6.5 ppm the characteristic hydroxymethyl peaks as a doublet at 5.4 ppm for the methylene protons and a signal for the OH proton overlapping with the aromatic protons.

The products of refluxing either 6-methyl-5-(4-methoxy phenyl)-5,6-dihydro-1,2,4-triazolo[4,3-c]quinazoline-3-thiol (**IV$_d$**) or 6-methyl-5-phenyl-5,6-dihydro-1,2,4-triazolo[4,3-c]quinazoline-3-thiol (**IV$_e$**) with formaldehyde gave mass spectrum identical to that of 3-hydroxymethyl-6-methyl-5,6-dihydro-1,2,4-triazolo[1,5-c]quin-azolin-2-thione (**VI$_a$**). This variation in the product of the reaction with the change of 5-aryl substituent of (IV) prompted us to postulate a mechanism for such reaction.



The presence of electron donating group like p-methoxy probably enhances the expel of the aromatic moiety by its ability to stabilize the first intermediate by resonance and the more reactive methylene cation replaces the aromatic moiety. Thus, p-methoxyphenyl gave the product in 2 hours but unsubstituted phenyl required 24 hours to give the product due to absence of a stabilizing electron donating group.

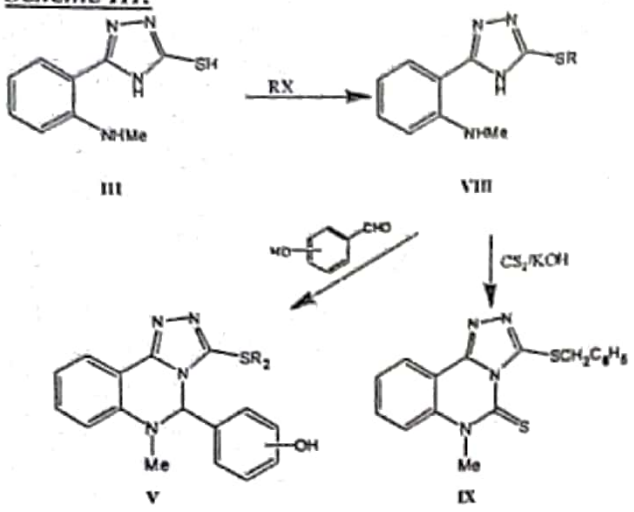
On the other hand presence of electron withdrawing group like p-nitro, p-bromo or p-chloro depress the exchange, instead the following may occur:



VII$_a$

In addition, electronic effect of p-nitro group probably reduces the availability of the electron pair on N_3 thus reduces the rate of formation of hydroxymethyl derivative which is formed after 7 hours of reflux.

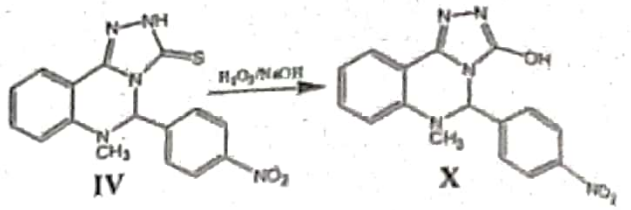
Scheme III:



The synthesis of thioether of 5-(2-methylaminophenyl)-1,2,4-triazol-3-thiol (III) was intended to specifically alkylate the thiol group and prevent other groups from interfering with this reaction. This new intermediate (VIII) was used in the synthesis of 3-alkylthio-5-(4-hydroxyphenyl)-6-methyl-5,6-dihydro-1,2,4-triazolo-[4,3-c]quinazoline (V_{kJ}) and 3-alkylthio-5-(2-hydroxyphenyl)-6-methyl-5,6-di-hydro-1,2,4-triazolo[4,3-c]quinazoline (V_{kJ}) by their condensation with 4-hydroxybenzaldehyde or 2-hydroxybenzaldehyde respectively, where trying to synthesize thioethers from triazoloquinazoline in such compounds will cause etherification of the aromatic hydroxyl group, so, initial etherification followed by internal Mannich reaction is a must sequence to obtain the required compound with free aromatic hydroxyl group.

Also, the novel 3-benzylthio-6-methyl-1,2,4-triazolo[4,3-c]quinazolin-5[6H]-thione (IX) is prepared by refluxing 5-(2-methylamino phenyl)-3-benzylthio-[4H]-1,2,4-triazol ($VIII_c$) with carbon disulfide in ethanolic potassium hydroxide for 5 hours. The structure of the synthesized compound (IX) was characterized by disappearance of the characteristic NH stretching vibration band at 3400 cm^{-1} in its IR spectrum.

Trials to prepare the target compound (X) adapting the same sequence illustrated in Scheme I but using semicarbazide instead of thiosemicarbazide where failed. So, the novel compound (X) was synthesized by following the procedure of oxo-desulfuration[14] to desulfurize 6-methyl-5-(4-nitrophenyl)-5,6-dihydro-1,2,4-triazolo[4,3-c]quinazolin-3[2H]-thione (IV_a) with 30% hydrogen peroxide in 5% sodium hydroxide at room temperature followed by neutralization with acetic acid.



Compound X can exist in either of two forms, the keto form or the enol form. IR spectrum showed that compound X exists in the enol form where it showed the characteristic hydroxyl stretching band at 3300 cm^{-1} and also the absence of the amidic carbonyl stretching band at 1690 cm^{-1}.

PHARMACOLOGICAL SCREENING

Preliminary screening in mice:

All the new 1,2,4-triazolo[4,3-c]quinazoline and 5,6-dihydro-1,2,4-triazolo[1,5-c]quinazoline derivatives were tested using conscious adult male mice weighing 18-22 gm. The compounds were dissolved in propylene glycol. The changes in the behavior of mice after intrapretonial injection of the tested compound in a dose of 1.5 mg/kg were observed before and for 60 minutes after the administration of the compounds. The following compounds showed noticeable CNS effects:

Compounds VI_a and VI_b produced high stimulant effect observed after 2 minutes of administration in the form of increased locomotor activity, abnormal rapid gate, walking on toes, tail erection and tremors in the muscles of the back legs. While compounds IV_a, V_b VI_d and **X** showed moderate stimulation starting after 10 minutes of administration, observed in the form of abnormal rapid gate, walking on toes and tail erection but no tremors were observed.

Screening in group of mice:

Compounds VI_a, VI_b and VI_d which showed the highest activities in the preliminary screening were subjected to screening on groups of mice. Each compound was injected intrapretonially in a dose of 1.5 mg/kg in 5 different mice and the observed changes in behavior were recorded. Where compounds VI_a and VI_b showed the highest CNS stimulating effect on mice observed in the form of increased locomotor activity, tail erection, muscle contraction and abnormal rapid gate. All these changes were started after 5 to 10 minutes of the compound administration. While compound VI_d showed lower degree of stimulation where the observed changes started 20 minutes after administration and the increased locomotor activity was less than compounds VI_a and VI_b. In addition no muscle contractions were observed.

Electroencephalographic recording in rabbits:

Based on the results obtained from mice, EEG recording in conscious adult male rabbits weighing 1.5-2 kg was obtained. Compound VI_a was dissolved in propylene glycol. The prepared rabbit with

implanted electrodes was injected intravenously in the marginal ear vein in a dose of 1.5 mg/kg.

Electroencephalographic recording:

The rabbits were fixed to the holder then placed in a darkened chamber in a quiet room and left without disturbance for at least 30 minutes before starting the EEG recording prior to the administration of the drugs.

An eight-channel ink-writing electroencephalogram (MEDLEC TM 500) was used for recording the electrical activity of the brain. The spontaneous brain biopotentials were recorded from the cortical and subcortical electrodes; also the evoked potentials were studied by subjecting the animals to photic and sonic stimulations. Photic stimulation was delivered in the form of repeated flashes of light for 5 seconds, whereas sonic stimulus was delivered in the form of a continuous buzz for about 5 seconds. The spontaneous EEG pattern and the evoked potentials were recorded before drug administration and after different time intervals according to the experimental design.

RESULTS AND DISCUSSION

The Changes in the spontaneous EEG pattern and evoked potential were recorded and interpreted. Compound **VI$_a$** (3-hydroxymethyl-6-methyl-5,6-dihydro-1,2,4-triazolo[1,5-c]quinzolin-2[3H]-thione) belongs to the c-annellated triazoloquinazoline group. Its administration in conscious rabbits showed a generalized increase in the number of alpha and beta waves (rapid waves), a decrease in the number of delta and theta waves (slow waves), an increase in the total wave's number and a decrease in the mean voltage. Moreover, evoked potential showed an increase in both sonic and photic after effects. All these changes indicated that compound **VI$_a$** in a dose of 1.5 mg/kg induced a stimulant effect.

The work of Chen and Hutchison[1,2] and Francis et al.[15] showed that compounds of this series have a tendency to act as benzodiazepine receptor ligands, where they may act as BZR agonists showing CNS depressant activity, BZR antagonists or inverse agonist having stimulatory effects. Moreover, the work of Francis et al.,[8] Ghai et al.[9] and Kim et al.[10] revealed that this system have stimulatory effect by acting as adenosine antagonist.

CONCLUSION

Preliminary screening on mice gave indication about the pharmacologically active compounds on the CNS.

From the results of both preliminary screening and screening in groups of mice compounds **VI$_a$**, **VI$_b$** and **VI$_d$** showed noticeable CNS stimulant effects. All these compounds belong to the 3-hydroxymethyl-5,6-dihydro-1,2,4-triazolo[1,5-c]quinazolin-2-thione. So, probably the presence of 3-hydroxymethyl group can attain CNS stimulatory effect and probably plays a role in the binding of these compounds with the receptor through hydrogen bond formation.

Most other compounds which lacked the hydroxymethyl group were inactive and only few showed weak stimulating effect namely compounds **IV$_f$**, **V$_l$**, and **X**. These compounds need more investigations to conclude a structure-activity relationship for this group of compounds.

EXPERIMENTAL

Chemistry:

Melting point were determined with a Gallenkamp melting point apparatus and are uncorrected. IR spectra (KBr, cm^{-1}) were determined on a Pye-Unicam SP-100 spectrophotometer, ^1H NMR spectra were recorded on a varian EM-390, 90 MHz spectrophotometer in DMSO-d_6 or $CDCl_3$ as a solvent and TMS as an internal standard (chemical shift in δ, ppm), and mass spectra were determined using a Mat 1125 at 70 eV spectrometer (Microanalytical center, Cairo University, Cairo, Egypt). Elemental analyses were performed in Organic Microanalytical Lab., National Research Center, Cairo, Egypt.

2-[2-(Substituted amino)benzoyl] hydrazinecarbothioamide (II$_{a,b}$):

A mixture of N-substituted isatoic anhydride I$_{a,b}$(0.05 mol) and thiosemicarbazide (4.55 g, 0.05 mol) in glacial acetic acid (20 ml) was stirred at room temperature for 2 hours. The separated solid was filtered, dried and recrystallized from ethanol to give the titled compounds

Compound IIa, R=CH3: [m.p. 218-219 °C, yield (70%)].
Analysis for $C_9H_{12}N_4OS$ (224):
Calcd: %C, 48.20; %H, 5.35; %N, 24.98
Found: %C, 47.86; %H, 5.56, %N, 24.68
IR (cm^{-1}): 3399, 3347 (NH), 3190 (NH_2), 2980 (CH aliphatic), 1640 (amidic C=O).

Compound IIb, R= m-$(CF_3)C_6H_4$: m.p. 210-211°C, yield (57%)
Analysis for $C_{15}H_{13}F_3N_4OS$ (354):
Calcd: %C, 50.48; %H, 3.70; %N, 15.81
Found: %C, 50.85; %H, 3.59; %N, 15.69

5-[2-(Substituted amino)phenyl]-4H-1,2,4-triazol-3-thiol (III$_{a,b}$) :

2-[2-(Substitutedamino)benzoyl]hydrazinecarbothioamide **III$_{a,b}$** (0.05 mol) was dissolved in 2N sodium hydroxide (20 ml) and heated under reflux for 2 hours. The solution was cooled on ice and neutralized carefully with hydrochloric acid. The solid precipitate was collected by filtration, washed thoroughly with water, dried and recrystallized from a suitable solvent (aqueous dioxane in case of **III$_a$** and ethanol in case of **III$_b$**) to give the titled compounds (Table 1).

Compound III_a, R=CH_3: MS analysis (*m/z*, M^+): 206; IR (cm^{-1}): 3358, 3095 (NH), 2964 (CH aliphatic), 1615 (C=N).
Compound II_b, R= m-(CF_3) C_6H_4: MS analysis (*m/z*, M^+): 336; IR (cm^{-1}): 3357, 3094 (NH), 3085 (CH aromatic), 1614 (C=N).

6-Substituted-5-(4-substitutedphenyl)-5,6-dihydro-1,2,4-triazolo[4,3-c]quinazoline-3-thiol (IV_{a-f}):

A mixture 5-[2-(Substituted amino) phenyl]-4H-1,2,4-triazol-3-thiol **III** (0.05 mol) and the appropriate p-substituted benzaldehyde (0.05 mol) in acetic acid (20 ml) was heated under reflux with stirring for 2 hours. The crystalline solid separated on cooling was collected by filtration, dried and recrystallized from ethanol to give the titled compounds (Table 2).
Compound **IV_a**; R=CH_3, R'=4-NO_2: ^{1}H-NMR (DMSO-D6, δ, ppm): 3.0 (s, 3H, N-CH_3), 6.8- 8.2 (m, 9H, benzylic proton overlapping with 8 aromatic protons); MS analysis (*m/z*, M^+) of compound No. **IV_a**: 339.
Compound IV_b; R=CH_3, R'=4-Cl: ^{1}H-NMR (DMSO-D6, δ, ppm): 2.97 (s, 3H, N-CH_3), 6.67 (s, 1H, benzylic proton), 6.8-7.8 (m, 8H, aromatic protons).
Compound IV_c; R=CH_3, R'=4-Br: MS analysis (*m/z*, M+2): 374.

3-Alkylthio-6-methyl-5-(4-substitutedphenyl)-5,6-dihydro-1,2,4-tria-zolo[4,3-c]quinazoline (V_{a-b}):

The appropriate alkyl halide (0.002 mol) was added to a solution of 6-methyl-5-(4-substituted phenyl)-5,6-dihydro-1,2,4-triazolo[4,3-c]quina-zoline-3-thiol **IV** (0.002 mol) and sodium hydroxide (0.1 g) in water (10 ml). The solution was stirred at room temperature for 2 hours. The separated solid was collected by filtration, dried and recrystallized from ethanol to give the titled compounds (Table 2).
Compound **V_a**; R=CH_3, R'=4-NO_2, R_2= CH_3: ^{1}H-NMR (DMSO-D_6, δ, ppm): 2.5(s, 3H, S-CH_3), 2.9 (s, 3H, N-CH_3), 7.0 (s, 1H, benzylic proton), 6.8-8.2 (m, 8H, aromatic protons).

3-Alkylthio-5-(2-methylaminophenyl)-4H-1,2,4-triazol ($VIII_{a-c}$):

To a solution of 5-[2-(methylamino)phenyl]-4H-1,2,4-triazol-3-thiol **III_a** (0.82 g. 0.004 mol) and sodium hydroxide (0.2 g) in water (10 ml), the appropriate alkyl halide (0.004 mol) was added. The solution was stirred at room temperature for 2 hours. The separated solid was collected by filtration, dried and recrystallized from ethyl acetate to give the titled compounds (Table 1).
Compound **$VIII_c$**; R=CH_3, R_2=$CH_2C_6H_5$: IR (cm^{-1}): 3325, 3216 (NH), 3062 (CH aromatic), 2986 (CH aliphatic), 1614 (C=N).

3-Alkylthio-5-(hydroxyphenyl)-6-methyl-5,6-dihydro-1,2,4-triazolo [4,3-c]quinaz-oline (V_{i-j}):

Mixture of 3-alkylyhio-5-(2-methylaminophenyl)-4H-1,2,4-triazol **VIII** (0.005 mol) and the appropriate hydroxybenzaldehyde (0.6 g, 0.005 mol) in acetic acid (20 ml) was heated under reflux for 2 hours with stirring. The crystalline solid separated on cooling was collected by filtration, dried, and recrystallized from ethanol to give the titled compounds (Table 2).
Compound **V_i**; R=CH_3, R'=4-OH, R_2= CH_3 IR (cm^{-1}) 3094 (OH), 3017 (CH aromatic), 2974 (CH aliphatic), 1612 (C=N).
Compound **Vj**; R=CH_3, R'=4-OH, R_2= CH_2-CH=CH_2: ^{1}H-NMR (DMSO-D_6, δ, ppm): 2.89 (s, 3H, N-CH_3), 3.7 (d, 2H, S-CH_2), 5.0 (d, 1H, one of the two protons of CH=CH_2), 5.2 (d, 1H, the other proton of CH=CH_2), 5.9 (m, 1H, CH_2-CH=CH_2), 6.6-7.8 (m, 9H, 8 aromatic protons overlapping with the benzylic proton), 9.7 (s, 1H, OH).

3-Hydroxymethyl-5,6-disubstituted-5,6-dihydro-1,2,4-triazolo[1,5-c]quinazolin-2-thione (VI_{a-d}):

A mixture of 5-[2-(Substituted amino) phenyl]-4H-1,2,4-triazol-3-thiol **III** (0.01 mol) or 6-Substituted-5-(4-substituted phenyl)-5,6-dihydro-1,2,4-triazolo[4,3-c]quinazoline-3-thiol **(IV_{a-c})** and formaldehyde (1 ml) in ethanol (15 ml) was heated under reflux for 1 hour to give compounds ($VI_{a,b}$) or ($VI_{c,d}$) respectively . The crystalline solid separated on cooling was collected by filtration, dried and recrystallized from ethanol to give the titled compounds (Table 3).

Compound **VI_a**; R=CH_3, R_1=H: ^{1}H-NMR (DMSO-D_6, δ, ppm): 2.9 (s, 3H, N-CH_3), 5.0 (s, 2H, methylene protons), 5.4 (d, 2H, CH_2-OH), 6.9-7.7 (m, 5H, OH proton overlapping with 4 aromatic protons); IR (cm^{-1}): 3304 (OH), 2959 (CH aliphatic), 1614 (C=N); MS analysis (*m/z*, M^+): 248.
Compound **VI_b**; R= m-(CF_3)C_6H_4, R_1=H: ^{1}H-NMR (DMSO-D_6, δ, ppm) 5.4 (d, 2H, CH_2-OH), 5.6 (s, 2H, methylene protons), 6.9-7.9 (m, 9H, OH proton overlapping with 8 aromatic protons).
Compound **VI_c**; R=CH_3, R_1=4-$NO_2C_6H_4$; ^{1}H-NMR (DMSO-D_6, δ, ppm): 3.0 (s, 3H, CH_3), 5.4 (d, 2H, CH_2-OH), 6.8 (s, 1H, benzylic proton), 6.9-7.8 (m, 9H, 8 aromatic protons overlapping with OH).
Compound **VI_d**; R=CH_3, R_1=4-ClC_6H_4; ^{1}H-NMR (DMSO-D_6, δ, ppm): 2.9 (s, 3H, CH_3), 5.4 (d, 2H, CH_2-OH), 6.6 (s, 1H, benzylic proton), 6.8-7.8 (m, 9H, 8 aromatic protons overlapping with OH).

6-Methyl-5-(4-substituted phenyl)-5,6-dihydro-1,2,4-triazolo[1,5-c] quinazoline-2-thiol ($VII_{a,b}$):

Mixture of 6-methyl-5-(4-substituted phenyl)-5,6-dihydro-1,2,4-triazolo[4,3-c]quinazoline-3-thiol **IV$_{a,c}$** (0.002 mol) and formaldehyde (1 ml) in ethanol (15 ml) and acetic acid (0.5 ml) was heated under reflux for 1 hour. The formed product was separated by addition of water, then collected by filtration, dried and recrystallized from ethanol to give the titled compounds (Table 3).

Compound **VII$_a$**; R=CH_3, R_1=4-$NO_2C_6H_4$; ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.0 (s, 3H, CH_3), 6.5 (s, 1H, benzylic proton), 6.5-8.1 (m, 8H, aromatic protons); IR (cm^{-1}): 3075 (CH aromatic), 2950 (CH aliphatic), 1613 (C=N); MS analysis (m/z, M^+): 339.
Compound **VII$_b$**; R=CH_3, R_1=4-BrC_6H_4: IR (cm^{-1}): 3054 (CH aromatic), 2995 (CH aliphatic), 1612 (C=N); MS analysis (m/z, M+2): 374.

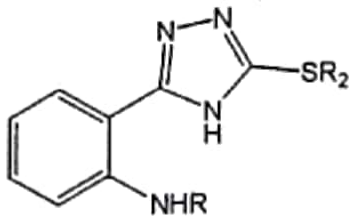
3-Benzylthio-6-methyl-1,2,4-triazolo[4,3-c]quinazolin-5[6H]-thione (IX):

To a solution of 3-benzylthio-5-(2-methylaminophenyl)-4H-1,2,4-triazol **VIII$_c$** (1.48 g, 0.005 mol) and potassium hydroxide (0.28 g, 0.005 mol) in ethanol (20 ml) carbon disulfide (0.4 g, 0.005 mol) was added and the solution was heated under reflux for 5 hours. The crystalline solid separated on cooling was filtered, dried and recrystallized from ethanol [m.p. 159-160 °C, yield (79%)].
Analysis for $C_{17}H_{14}N_4S_2$:
Calcd: %C, 60.33; %H, 4.17; %N, 16.55
Found: %C, 59.95; %H, 4.17; %N, 16.37
IR (cm^{-1}): 3025 (CH aromatic), 2927 (CH aliphatic), 1621 (C=N).

3-Hydroxy-6-methyl-5-(4-nitrophenyl)-5,6-dihydro-1,2,4-triazolo[4,3-c]quinazoline (X):

6-Methyl-5-(4-nitrophenyl)-5,6-dihydro-1,2,4-triazolo[4,3-c]quina-zoline-3-thio **IV$_a$** (0.34 g, 0.001 mol) was dissolved in 5% w/v sodium hydroxide (20 ml). With stirring, 30% hydrogen peroxide solution (20 ml) was added at room temperature. The mixture was then acidified with acetic acid, the resultant precipitate was washed with water and recrystallized from ethanol [m.p. > 300 °C, yield (45%)].
Analysis for $C_{16}H_{13}N_5O_3$:
Calcd: %C, 59.55; %H, 4.05; %N, 21.66
Found: %C, 59.90; %H, 4.22; %N, 21.46
IR (cm^{-1}): 3467 (OH), 3078 (CH aromatic), 2965 (CH aliphatic), 1617 (C=N); MS analysis (*m/z*, M^+): 323.

Table 1: 3-alkylthio-5-[2-(Substituted amino) phenyl]-4H-1,2,4-triazol



Com p. No.	R	R2	Yield %	m.p. °C	Molecular Formula (M.wt)	Elemental analysis		
						%	Calcd	found
III$_a$	CH_3	H	93.5	>300	$C_9H_{10}N_4S$ (206)	C H N	52.41 4.89 27.16	52.18 4.97 27.26
III$_b$	m-$(CF_3)C_6H_4$	H	91.2	282-284	$C_{15}H_{11}F_3N_4S$ (336)	C H N	53.57 3.30 16.66	53.75 3.43 16.29
VIII$_a$	CH_3	CH_3	69	110-112	$C_{10}H_{12}N_4S$ (220)	C H N	54.52 5.49 25.43	54.00 5.39 25.37
VIII$_b$	CH_3	CH_2-CH=CH_2	67.3	100-102	$C_{12}H_{14}N_4S$ (246)	C H N	58.51 5.73 22.74	58.35 6.01 22.68
VIII$_c$	CH_3	$CH_2C_6H_5$	73.2	122-123	$C_{16}H_{16}N_4S$ (296)	C H N	64.84 5.44 18.90	64.66 5.46 18.79

Table 2: 3-alkylthio-6-substituted-5-(4-substituted phenyl)-5,6-dihydro-1,2,4-tri-azolo[4,3-c]quinazoline

Comp. No.	R	R'	R_3	Yield %	m.p. °C	Molecular Formula (M.wt.)	Elemental analysis %	Calcd	found
IV$_a$	CH_3	p-NO_2	H	85.4	233-235	$C_{16}H_{13}N_5O_2S$ (339)	C	56.63	56.31
							H	3.86	4.06
							N	20.64	20.63
IV$_b$	CH_3	p-Cl	H	97.9	219-220	$C_{16}H_{13}ClN_4S$ (328)	C	58.44	58.17
							H	3.98	4.03
							N	17.04	16.97
IV$_c$	CH_3	p-Br	H	80.6	266-267	$C_{16}H_{13}BrN_4S$ (372)	C	51.48	51.12
							H	3.51	3.63
							N	15.01	14.77
IV$_d$	CH_3	p-OCH_3	H	84.6	199-200	$C_{17}H_{16}N_4OS$ (324)	C	62.94	63.08
							H	4.97	5.25
							N	17.27	17.20
IV$_e$	CH_3	H	H	73.5	257-258	$C_{16}H_{14}N_4S$ (294)	C	65.28	65.01
							H	4.79	4.88
							N	19.03	18.98
IV$_f$	m-$(CF_3)C_6H_4$	H	H	65.7	235-237	$C_{22}H_{15}F_3N_4S$ (424)	C	62.25	62.04
							H	3.56	3.67
							N	13.20	13.14
V$_a$	CH_3	p-NO_2	CH_3	85.7	154-155	$C_{17}H_{15}N_5O_2S$ (353)	C	57.78	57.61
							H	4.28	3.91
							N	19.82	19.60
V$_b$	CH_3	p-Cl	C_2H_5	61.8	119-120	$C_{18}H_{17}ClN_4S$ (356.8)	C	60.58	59.78
							H	4.80	4.65
							N	15.70	15.71
V$_c$	CH_3	p-Cl	$CH_2C_6H_5$	69	127-128	$C_{23}H_{19}ClN_4S$ (418.9)	C	65.94	65.21
							H	4.57	4.38
							N	13.37	13.31
V$_d$	CH_3	p-Cl	CH_2-$CH=CH_2$	64.3	111-112	$C_{19}H_{17}ClN_4S$ (368.8)	C	61.86	61.71
							H	4.65	4.57
							N	15.19	14.99
V$_e$	CH_3	p-Br	CH_3	70	155-157	$C_{17}H_{15}BrN_4S$ (387)	C	52.72	52.48
							H	3.90	3.63
							N	14.47	14.37
V$_f$	CH_3	p-Br	CH_2-$CH=CH_2$	69.1	110-112	$C_{19}H_{17}BrN_4S$ (413)	C	55.21	54.77
							H	4.15	4.16
							N	13.55	13.39
V$_g$	CH_3	p-OCH_3	CH_2-$CH=CH_2$	79.7	78-79	$C_{20}H_{20}N_4OS$ (364)	C	65.91	65.43
							H	5.53	5.29
							N	15.37	15.24
V$_h$	CH_3	H	CH_2-$CH=CH_2$	73.7	83-84	$C_{19}H_{18}N_4S$ (334)	C	68.23	68.04
							H	5.42	5.00
							N	16.75	16.72
V$_i$	CH_3	p-OH	CH_3	79.5	270-271	$C_{17}H_{16}N_4OS$ (324)	C	62.94	62.49
							H	4.97	4.63
							N	17.27	17.03
V$_j$	CH_3	p-OH	CH_2-$CH=CH_2$	69	234-236	$C_{19}H_{18}N_4OS$ (350)	C	65.12	64.85
							H	5.18	4.96
							N	15.99	15.79
V$_k$	CH_3	o-OH	$CH_2C_6H_5$	75	230-232	$C_{23}H_{20}N_4OS$ (400.5)	C	68.98	69.14
							H	5.03	4.80
							N	13.99	13.68
V$_l$	CH_3	o-OH	CH_2-$CH=CH_2$	56	207-208	$C_{19}H_{18}N_4OS$ (350)	C	65.12	65.89
							H	5.18	4.65
							N	15.99	15.81

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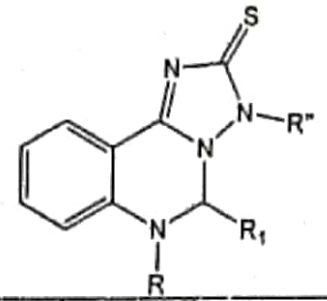
Table 3: 5,6-dihydro-1,2,4-triazolo[1,5-c]quinazolin-2-thione:



Comp. No.	R	R_1	R''	Yield %	m.p. °C	Molecular Formula (M. wt.)	Elemental analysis		
							%	Calcd	found
VI$_a$	CH_3	H	CH_2OH	73.4	184-185	$C_{11}H_{12}N_4OS$ (248)	C H N	53.21 4.87 22.56	53.10 5.08 22.43
VI$_b$	m-$(CF_3)C_6H_4$	H	CH_2OH	89.2	198-200	$C_{17}H_{13}F_3N_4OS$ (378)	C H N	53.96 3.46 14.81	54.13 3.92 14.78
VI$_c$	CH_3	p-$NO_2C_6H_5$	CH_2OH	65.5	177-178	$C_{17}H_{15}N_5O_3S$ (369)	C H N	55.27 4.09 18.96	54.72 4.28 18.80
VI$_d$	CH_3	p-ClC_6H_5	CH_2OH	80.7	169-170	$C_{17}H_{15}ClN_4OS$ (358)	C H N	56.90 4.21 15.61	57.02 4.37 15.48
VII$_a$	CH_3	p-$NO_2C_6H_5$	H	92.3	51-153	$C_{16}H_{13}N_5O_2S$ (339)	C H N	56.63 3.86 20.64	56.96 3.80 20.58
VII$_b$	CH_3	p-BrC_6H_5	H	83.5	186-187	$C_{16}H_{13}BrN_4S$ (372)	C H N	51.48 3.51 15.0	51.27 3.55 15.24

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تشييد مشتقات 4،2،1-تريازولوكينازولين الجديدة ودراسة تأثيرها على الجهاز العصبى المركزى

نهى إبراهيم زيدان – عبدالله أحمد الشنوانى – صبحى محمد العدل – سامى مجاهد صقر

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تم فى هذا البحث تشييد مركبات 4،2،1-تريازولو[4،3-ج]كينازولين-3-ثيول (IV_{a-f}) وثيوايثيراتها (V_{a-f}) ومركبات 4،2،1-تريازولو[1،5-ج]كينازولين-2-ثيون (VI_{a-d}) و ($VII_{a,b}$) . وتم تحضير هذه المركبات بتفاعل مشتقات الأيزاتويك اللامائية (I) مع مادة ثيوسيمى كاربازيد وتم حولقة الناتج ($II_{a,b}$) باستخدام هيدروكسيد الصوديوم لتكوين مشتقات التريازول ثيول ($III_{a,b}$) وثيوايثيراتها ($VIII_{a-c}$) التى تم حولقتها بالألدهيدات المختلفة بما فى ذلك الفورمالدهيد الذى ساعد استخدامه فى تحضير مشتقات 4،2،1-تريازولو[1،5-ج]كينازولين-2-ثيون . كما تم حولقة الثيوايثيرات (VIII) باستخدام الكربون ثنائى الكبريت للحصول على مشتق 4،2،1-تريازولو[4،3-ج]كيناولين-5(6يد)ثيون (IX) . وتم تحضير 3-هيدروكسى-4،2،1-تريازولو[4،3-ج]كينازولين (X) من مشتق الثيون (IV_a) وذلك باستخدام فوق أكسيد الهيدروجين وهيدروكسيد الصوديوم .

وقد تم اختبار بعض مشتقات التريازولوكينازولين الجديدة من حيث تأثيرها المنشط للجهاز العصبى المركزى وذلك بتسجيل التغيرات فى نشاط المخ الكهربى التى أجريت على الأرانب بعد حقنها الوريدى بالمواد المختارة حيث وجد أن لبعض المواد ا لمختبره نتائج ملحوظة .