Research Article

Design, Synthesis, Computer Modeling and Pharmacological Evaluation of Some New Condensed Pyrimidines

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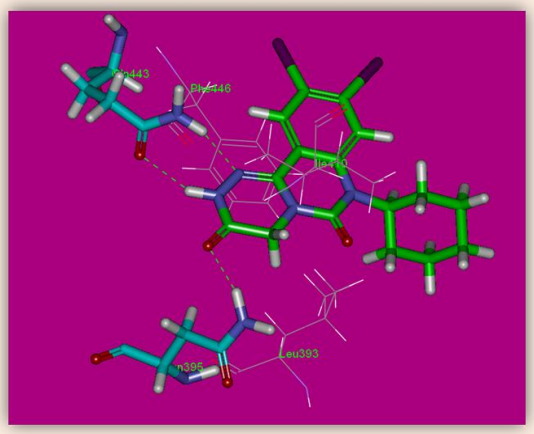
Abstract

Condensed pyrimidines are still being pharmacologically interesting compounds as many derivatives showed a broad spectrum of biological activities. Thus, some new quinazolino[1,2-c]qunazolin-13-ones and 2,3,4,5-tetrahydro-2,5-dioxo-1H-1,2,4-triazino[4,3-c]quiazolines were synthesized and characterized by both elemental and spectral analyses. Pharmacological evaluation of these derivatives showed that some vinyl derivatives of quinazolinoquinazolinone possess a significant hypnotic activity compared with phenobarbitone, whereas, other quinazolinoquinazolinones and triazinoquinazolines, showed mild non-narcotic analgesic activity compared with paracetamol.

Keywords: Quinazoline, triazinoquiazolines, vinyl quinazolinones, analgesic, anticonvulsant activity



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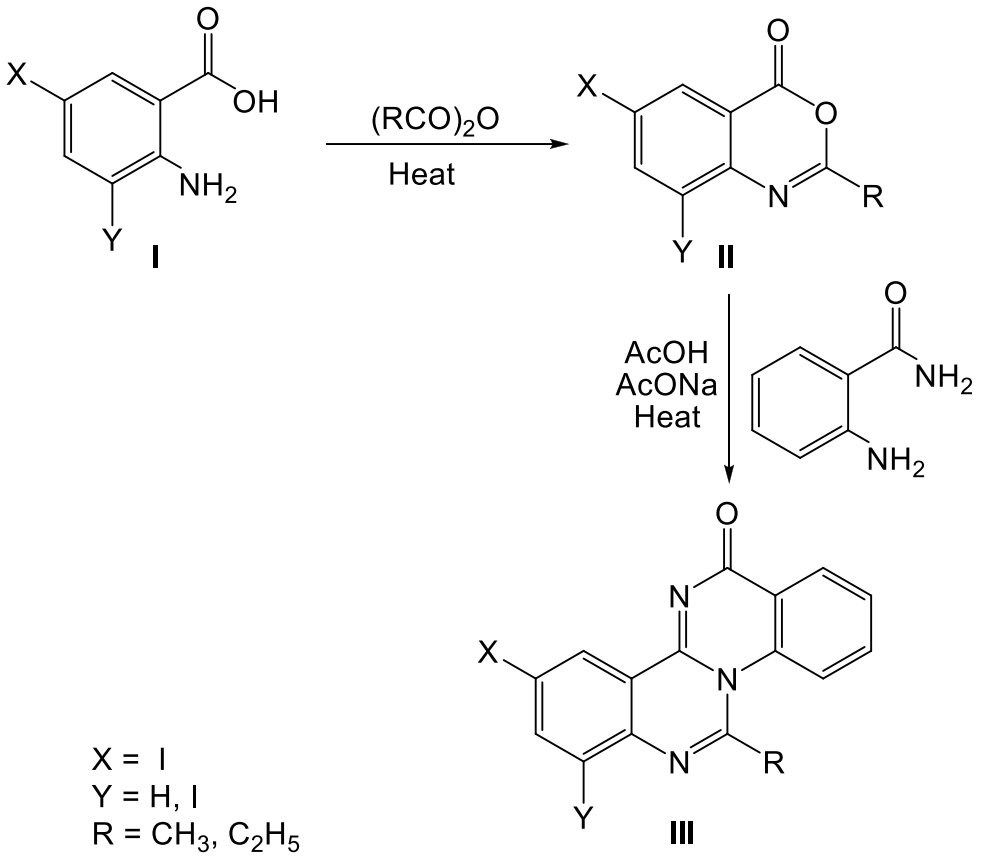
Introduction

In the last few years, the attention was oriented towards the synthesis and biological evaluation of some new classes of condensed pyrimidines as they exhibit a broad spectrum of biological activities [1-8]. Indeed, many of condensed pyrimidine derivatives have been reported to possess analgesic, antipyretic and anti-inflammatory activities [9-15]. On the other hand, many fused pyrimidines such as quinazolines are biologically versatile compounds possessing sedative-hypnotic, anticonvulsant, analgesic, anti-inflammatory, diuretic and other diverse activities [16-20]. In addition many triazines were reported to be analgesic and anti-inflammatory [21]. Moreover, it is well known that the methyl group at position -2 of quinazoline ring system possesses high reactivity and can be condensed with many aldehydes to afford the corresponding 2-vinyl derivatives [22] Many 2-vinyl quinazolinones were reported to possess a marked CNS depressant and muscle relaxant activities [23,24].

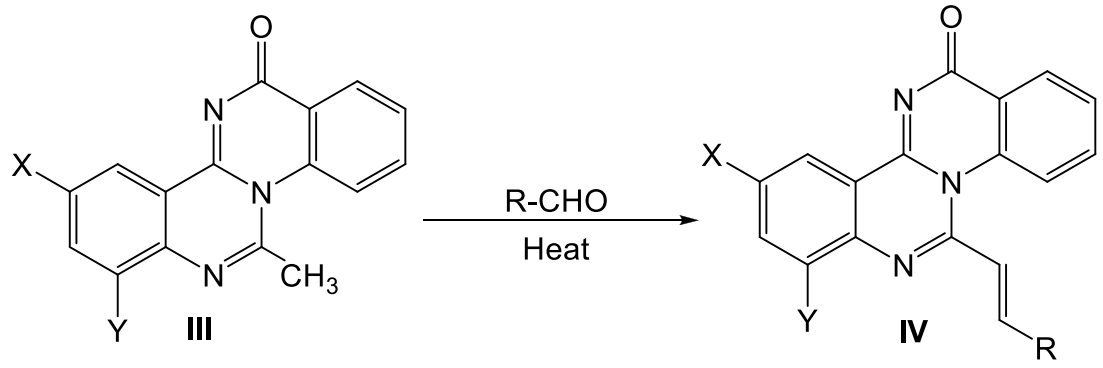
Accordingly, it seemed most interesting to synthesize some new quinazolinoquinazolinones (**III, IV**) and triazinoquinazolines **(X)** as new classes of condensed pyrimidines with the aim to evaluate their pharmacological activities. Scheme **1, 2** and **3** were adopted for the preparation of compounds (**III**, **IV** and **X**).

Experimental

All melting points were carried on Gallen Kamp melting point apparatus at Faculty of Pharmacy, Al-Azhar University and are uncorrected. The infrared spectra were recorded on Brucker-Vector-22F T-IR spectrophotometer using the potassium bromide disc technique at Faculty of Pharmacy, Al-Azhar University. The ^{1}H NMR spectra were recorded on Varian-Gemini-300-MHZ spectrophotometer using DMSO-d6 as a solvents and TMS as internal reference. The chemical shift values were recorded in δ ppm downfield the TMS signal. The mass spectra were recorded on AZH-ph-AR-XO_2 Mass spectrometer. Elemental analyses were performed on CHN analyzer. All spectral measurements have been performed at the Micro analytical Center, Cairo University, Cairo, Egypt.

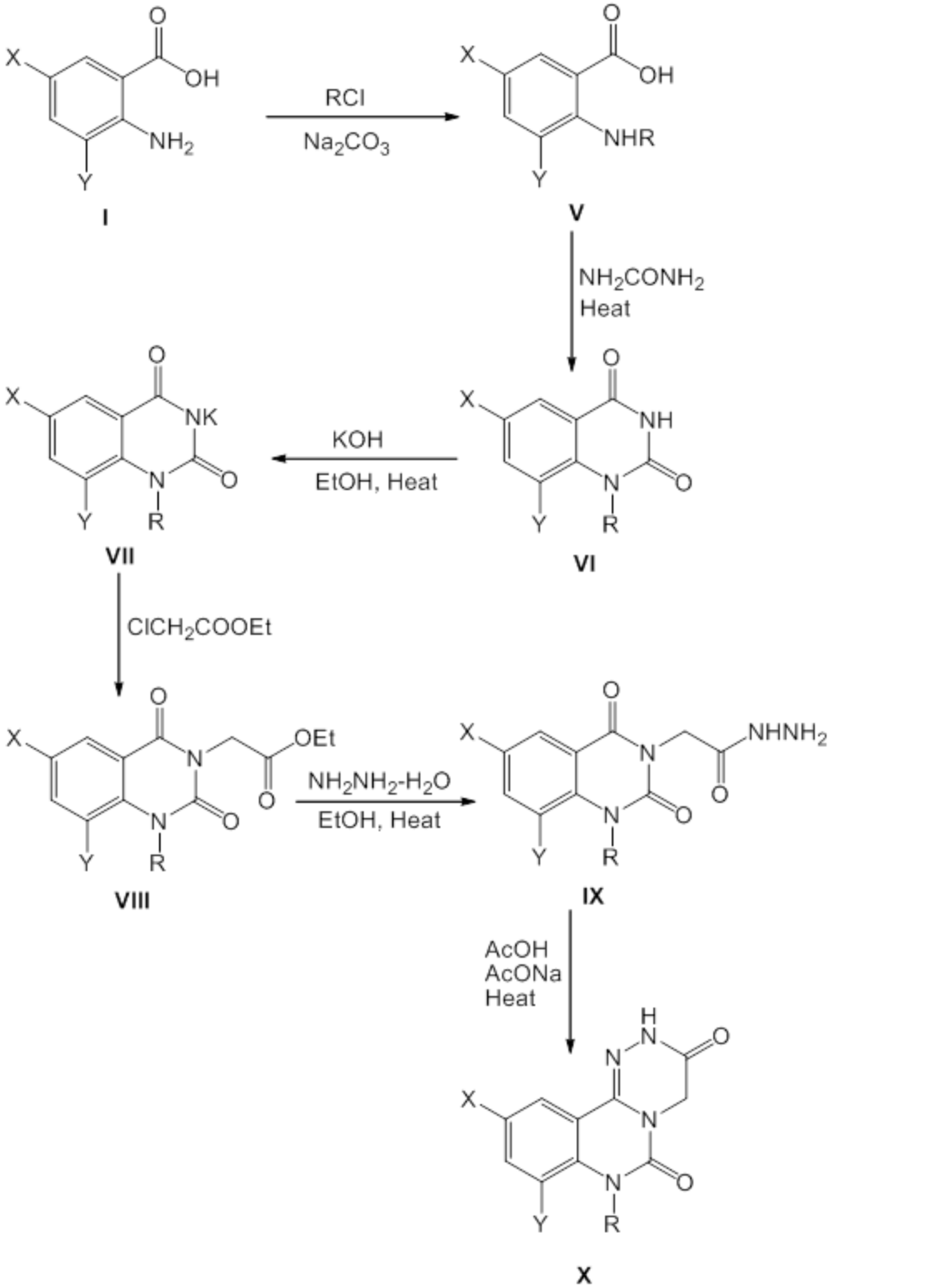


Scheme 1 Synthesis of 6-Alkylquinazolino[1,2-c] quinazolin-13-ones



X = I
Y = H, I
R` = CH_3, C_2H_5, 2-ClC_6H_4, 4-ClC_6H_4, 2,4-$(Cl)_2C_6H_4$, 2,6-$(Cl)_2C_6H_4$, 4-$(OCH_3)C_6H_4$
2,4-$(OCH_3)_2C_6H_4$, 4-$(OH)C_6H_4$.

Scheme 2 Synthesis of 6-(2-Substituted vinyl)quinazolino[1,2-c]quinazolin-13-ones



Scheme 3 Synthesis of 2,3,4,6-Tetrahydro-2.5-dioxo-1H-1,2,4-triazino[4,3-c]quinazolines

Anthranilic acids (I) and (V)

According to certain reported procedures, some substituted anthranilic acids were prepared such as 3,5-dibromooanthranilic acids [25] , 3,5-dichloroanthranilic acids [26,27] , 5-iodo- and 3,5-diiodoanthranilic acids, [28] , 3,5-dibromo-N-allyl-, 3,5-dichloro-N- allyl-, 5-iodo-N-allyl-, 3,5-diiodo-N-allyl-, 3,5-dibromo-N- benzyl-, 3,5-dichloro-N- benzyl-, 5-iodo-N- benzyl-, 3,5-diiodo-N- benzyl-, 3,5-dibromo-N-benzoyl-, 3,5-dichloro-N- benzoyl-, 5-iodo-N-benzoyl-, 3,5-diiodo-N-benzoyl -, 3,5-dibromo-N-(n-butyl)-, 3,5-dichloro-N- (n-butyl)-, 5-iodo-N-(n-butyl), 3,5-diiodo-N-(n-butyl)-, 3,5-dibromo-N-cyclohexyl-, 3,5-dichloro-N- cyclohexyl-, 5-iodo-N-cyclohexyl-, 3,5-diiodo-N-cyclohexyl-, 3,5-dibromo-N-ethyl-, 3,5-dichloro-N- ethyl-, 5-iodo-N-ethyl-, 3,5-diiodo-N-ethyl-, 3,5-dibromo-N-methyl-, 3,5-dichloro-N- methyl-, 5-iodo-N-methyl-, 3,5-diiodo-N-methyl-, 3,5-dibromo-N-(n-propyl)-, 3,5-dichloro-N- (n-propyl)-, 5-iodo-N-(n-propyl)-, 3,5-diiodo-N-(n-propyl)-, 3,5-dibromo-N-phenyl-, 3,5-dichloro-N- phenyl-, 5-iodo-N-phenyl-, 3,5-diiodo-N-phenyl anthranilic acids [29,30].

4H-3,1-benzoxazin-4-ones (II)

Using a reported procedure [31] the following benzoxazinones were prepared, 6-iodo-2-ethyl, 6,8-diiodo-2-ethyl, 6-iodo-2-methyl, 6,8-diiodo-2-methyl.

2,4(1H,3H)-Quinazolinediones (VI)

Following a reported procedure [32,33] many quinazolinediones (**VI**) were obtained namely 6,8-dibromo-1-allyl-, 1-benzoyl-, 1-benzyl-, 1-(n-butyl)-, 1-cyclohexyl-, 1-ethyl-, 1-methyl-, 1-phenyl- and 1-(n-propyl)-, 6,8-dichloro-1-allyl-, 1-benzoyl-, 1-benzyl-, 1-(n-butyl)-, 1-cyclohexyl-, 1-ethyl-, 1-methyl-, 1-phenyl- and 1-(n-propyl)-, 6-iodo-1-allyl-, 1-benzoyl-, 1-benzyl-, 1-(n-butyl)-, 1-cyclohexyl-, 1-ethyl-, 1-methyl-, 1-phenyl- and 1-(n-propyl)-, 6,8-diiodo-1-allyl-, 1-benzoyl-, 1-benzyl-, 1-(n-butyl)-, 1-cyclohexyl-, 1-ethyl-, 1-methyl-, 1-phenyl- and 1-(n-propyl)-2,4(1H,3H) quinazolinediones.

Potassium salts of 2,4 (1H,3H)-quinazolinediones (VII)

By application of the reported procedure [32,33] the potassium salts of quinazolinediones (**VI**) were prepared.

3-Ethoxycarbonylmethyl-2,4-(1H,3H)-quinazolinediones (VIII)

The following esters: 6,8-dibromo-1-allyl-3-ethoxy carbonylmethyl-, 1-benzoyl-3-ethoxy carbonylmethyl-, 1-benzyl-3-ethoxy carbonylmethyl-, 1-(n-butyl)-3-ethoxy carbonylmethyl-, 1-cyclohexyl-3-ethoxy carbonylmethyl-, 1-ethyl-3-ethoxy carbonylmethyl-, 1-methyl-3-ethoxy carbonylmethyl-, 1-(n-propyl)-3-ethoxy carbonylmethyl-, 1-phenyl-3-ethoxy carbonylmethyl-, 6,8-dichloro-1-allyl-3-ethoxy carbonylmethyl-, 1-benzoyl-3-ethoxy carbonylmethyl-, 1-benzyl-3-ethoxy carbonylmethyl-, 1-(n-butyl)-3-ethoxy carbonylmethyl-, 1-cyclohexyl-3-ethoxy carbonylmethyl-, 1-ethyl-3-ethoxy carbonylmethyl-, 1-methyl-3-ethoxy carbonylmethyl-, 1-(n-propyl)-3-ethoxy carbonylmethyl-, 1-phenyl-3-ethoxy carbonylmethyl-, 6-iodo-1-allyl-3-ethoxy carbonylmethyl-, 1-benzoyl-3-ethoxy carbonylmethyl-, 1-benzyl-3-ethoxy carbonylmethyl-, 1-(n-butyl)-3-ethoxy carbonylmethyl-, 1-cyclohexyl-3-ethoxy carbonylmethyl-, 1-ethyl-3-ethoxy carbonylmethyl-, 1-methyl-3-ethoxy carbonylmethyl-, 1-(n-propyl)-3-ethoxy carbonylmethyl-, 1-phenyl-3-ethoxy carbonylmethyl-, 6,8-diiodo-1-allyl-3-ethoxy carbonylmethyl-, 1-benzoyl-3-ethoxy carbonylmethyl-, 1-benzyl-3-ethoxy carbonylmethyl-, 1-(n-butyl)-3-ethoxy carbonylmethyl-, 1-cyclohexyl-3-ethoxy carbonylmethyl-, 1-ethyl-3-ethoxy carbonylmethyl-, 1-methyl-3-ethoxy carbonylmethyl-, 1-(n-propyl)-3-ethoxy carbonylmethyl-, 1-phenyl-3-ethoxy carbonylmethyl-2,4-(1H,3H)- quinazolinediones (**VIII**) were obtained following a reported procedure [32,33].

6-Alkylquinazolino[1,2-c] quinazolin-13-ones (III)

Anthranilamide (2.72 gm., 0.02 mole) was added to the appropriate benzoxazinone (**II**) (0.02 mole) dissolved in glacial acetic acid (30 ml) containing fused sodium acetate (2 gm.). The reaction mixture was refluxed for 8 hours, then poured over cold water with stirring and the solid product so obtained was recrystallized from ethanol (**Table 1**).

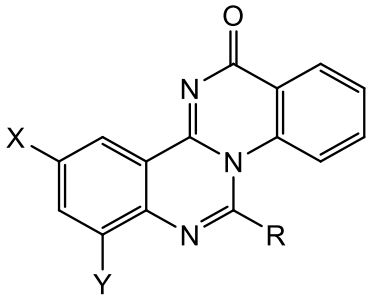


Figure 1 Chemical structure of compound III

Table 1 6-Alkylquinazolino[1,2-c]quinazolin-13-ones (III)

Comp. III	X	Y	R	Yield %	m.p. ˚C	M. Form. M. Wt	Elemental analysis C	H	N
1	I	H	CH_3	90	265-7	$C_{16}H_{10}N_3OI$	49.61	2.58	10.85
						387	49.82	2.67	10.87
2	I	H	C_2H_5	85	280-2	$C_{17}H_{12}N_3OI$	50.87	2.99	10.47
						401	50.91	2.81	10.62
3	I	I	CH_3	74	290-2	$C_{16}H_9N_3OI_2$	37.42	1.75	8.18
						513	37.48	1.89	8.35
4	I	I	C_2H_5	68	>300	$C_{17}H_{11}N_3OI_2$	38.70	2.08	7.96
						527	38.86	2.17	7.96

Table 2 ^{1}H NMR Spectral data of compounds (III)

Comp.	δ, multiplicity, protons
III.1	8.16 (1H, d, H-11.), 7.76-7.68 (2H, m, H-9,H-3), 7.64 (1H, d, H-1), 7.35 (1H, d, H-4), 7.17 (1H, d, H-8), 7.00 (1H, m, H-2), 2.17 (3H, s, CH_3).
III.2	8.12 (1H, d, H-11), 8.02 (1H, m, H-3.), 7.69 (1H, m, H-9), 7.45 (1H, d, H-1), 7.31 (1H, d, H-4), 7.17 (1H, d, H-8), 7.00 (1H, m, H-2), 2.74 (2H, m, CH_2), 1.28 (3H, t, CH_3).
III.3	8.24 (1H, d, H-9), 8.05 (1H, d, H-11.), 7.76 (1H, m, H-3), 7.64 (1H, d, H-1), 7.31 (1H, d, H-4), 7.00 (1H, m, H-2), 2.12 (3H, s, CH_3).
III.4	8.28 (1H, d, H-9), 8.05 (1H, d, H-11.), 7.76 (1H, m, H-3), 7.64 (1H, d, H-1), 7.31 (1H, d, H-4), 7.00 (1H, m, H-2), 2.68 (2H, m, CH_2), 1.24 (3H, t, CH_3).

Table 3 Mass Spectral data of compounds (III)

Comp.	m/z, (abound %)
III.1	387 (37.5) $M^{\cdot+}$), 372 (88.6) (M-CH_3), 105 (100.0) ($C_6H_5CO^+$).
III.2	401 (23.5) $M^{\cdot+}$), 386 (53.5) (M-CH_3), 372 (92.0) (M-C_2H_5), 105 (73.8) ($C_6H_5CO^+$), 90 (100) ($C_6H_4N^+$).
III.3	513 (62.3) $M^{\cdot+}$), 498 (27.8) (M-CH_3), 105 (62.7) ($C_6H_5CO^+$), 90 (100) ($C_6H_4N^+$).
III.4	527 (16.5) $M^{\cdot+}$), 512 (53.8) (M-CH_3), 498 (72.0) (M-C_2H_5), 105 (86.7) ($C_6H_5CO^+$), 90 (100) ($C_6H_4N^+$).

IR (III.1-4): (KBr, cm^{-1}) 1690-1700 cm^{-1} due to C=O stretching, 1600, 1560 and 1480 cm^{-1} are three bands of quinazoline ring system.

6-(2-Substituted vinyl)quinazolino[1,2-c]quinazolin-13-ones (IV)

The appropriate 6-methylquinazolino[1,2-c]quinazolin-13-ones (**III**) (0.01 mole) was mixed with suitable aldehyde (0.04 mole) and the reaction mixture was heated under anhydrous condition in an oil bath at 160-180˚C for two hours. The melted product was solidified on cooling and crystallized from ethanol to yield colorless needles (**Table 4**).

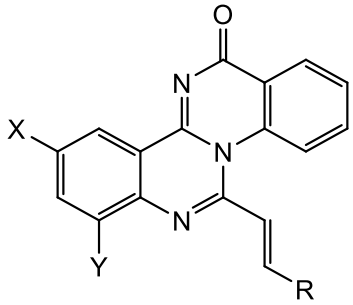


Figure 2 Chemical structure of compound IV

Table 4 6-(2-Substituted vinyl)quinazolino[1,2-c]quinazolin-13-ones (IV)

Comp. IV	X	Y	R	Yield %	m.p. °C	M. Form. / M.Wt	Elemental analysis		
							C	H	N
1	I	H	CH_3	90	265-7	$C_{18}H_{12}N_3OI$	52.30	2.90	10.16
						413	52.47	2.92	10.46
2	I	H	C_6H_5	87.5	273-5	$C_{23}H_{14}N_3OI$	58.10	2.94	8.84
						475	50.31	2.98	8.96
3	I	H	2-ClC_6H_4	92.4	290-2	$C_{23}H_{13}N_3OClI$	54.22	2.55	8.25
						509	54.38	2.76	8.41
4	I	H	4-ClC_6H_4	92.4	288-90	$C_{23}H_{13}N_3OClI$	54.22	2.55	8.25
						509	54.40	2.63	8.47
5	I	H	2,4-$Cl_2C_6H_3$	92.4	296-8	$C_{23}H_{12}N_3OCl_2I$	50.73	2.20	7.72
						544	50.84	2.43	7.92
6	I	H	2,6-$Cl_2C_6H_3$	92.4	297-9	$C_{23}H_{12}N_3OCl_2I$	50.73	2.20	7.72
						544	50.98	2.36	7.87
7	I	H	4-$(OCH_3)C_6H_4$	92.4	280-2	$C_{24}H_{16}N_3O_2I$	57.02	3.16	8.31
						505	57.27	3.35	8.50
8	I	H	2,4-$(OCH_3)_2C_6H_3$	92.4	290-2	$C_{25}H_{18}N_3O_3I$	56.07	3.36	7.85
						535	56.36	3.48	7.97
9	I	H	4-$(OH)C_6H_4$	92.4	278-80	$C_{23}H_{14}N_3O_2I$	56.21	2.85	8.55
						491	56.46	2.98	8.73
10	I	I	CH_3	85.7	>300	$C_{18}H_{11}N_3OI_2$	40.07	2.04	7.79
						539	40.32	2.19	7.85
11	I	I	C_6H_5	84.6	>300	$C_{23}H_{13}N_3OI_2$	45.92	2.16	6.98
						601	46.13	2.34	7.28
12	I	I	2-ClC_6H_4	94.1	>300	$C_{23}H_{12}N_3OClI_2$	43.46	1,88	6.61
						635	43.67	1.98	6.83
13	I	I	4-ClC_6H_4	92	>300	$C_{23}H_{12}N_3OClI_2$	43.46	1.88	6.61
						635	43.75	1.90	6.83
14	I	I	2,4-$Cl_2C_6H_4$	76	>300	$C_{23}H_{11}N_3OCl_2I_2$	41.19	1.64	6.27
						670	41.36	1.81	6.51
15	I	I	2,6-$Cl_2C_6H_4$	80	>300	$C_{23}H_{11}N_3OCl_2I_2$	41.19	1.64	6.27
						670	41.27	1.77	6.43
16	I	I	4-$(OCH_3)C_6H_4$	67	>300	$C_{24}H_{15}N_3O_2I_2$	45.64	2.37	6.65
						631	45.81	2.65	6.74
17	I	I	2,4-$(OCH_3)_2C_6H_4$	70.2	>300	$C_{25}H_{17}N_3O_3I_2$	45.38	2.57	6.35
						661	45.63	2.74	6.52
18	I	I	4-$(OH)C_6H_4$	78.5	>300	$C_{23}H_{13}N_3O_2I_2$	44.73	2.10	6.80
						617	44.88	2.29	6.97

Table 5 ^{1}H NMR Spectral data of compounds (IV)

Comp.	δ, multiplicity, protons
IV.1	8.06 (1H, d, H-11.), 7.68-7.0 (6H, m, aromatic H), 5.82 (1H, m, vinyl H), 5.19 (1H, d, vinyl H), 2.05 (3H, s, CH_3).
IV.2	8.10 (1H, d, vinyl H), 8.06-7.0 (12H, m, aromatic protons.), 7.20 (1H, d, vinyl H).
IV.3	8.06 (1H, d, H-11.), 7.68-7.0 (10H, m, aromatic H), 7.20 (1H, d, vinyl H), 6.70 (1H, d, vinyl H).
IV.4	8.20-7.0 (11H, m, aromatic H), 7.10 (1H, d, vinyl H), 6.50 (1H, d, vinyl H).
IV.5	8.12-7.20 (10 H, m, aromatic H), 7.20 (1H, d, vinyl H.), 6.65 (1H, d, vinyl H).
IV.6	8.10-7.18 (10 H, m, aromatic H), 7.10 (1H, d, vinyl H.), 6.50 (1H, d, vinyl H).

Table 6 Mass Spectral data of compounds (IV)

Comp.	m/z (abound %)
IV.1	413 (18) (M^+), 398 (100) (M-CH_3), 372 (33) (M-CH_3-CH=CH), 105 (76.5) ($C_6H_5CO^+$), 90 (100) ($C_6H_4N^+$).
IV.2	475 (34) (M^+), 398 (100) (M-C_6H_5), 372 (47) (M-C_6H_5-CH=CH), 105 (71) ($C_6H_5CO^+$), 90 (100) ($C_6H_4N^+$).
IV.7	505 (23) M^+), 397 (29) (M-OCH_3-C_6H_5), 371 (74) (M-OCH_3-C_6H_5-CH=CH), 105 (69) ($C_6H_5CO^+$), 90 (100) ($C_6H_4N^+$).
IV.9	491 (31) (M^+), 398 (48) (M-OH-C_6H_5), 371 (78) (M- OH-C_6H_5-CH=CH), 105 (82.5) ($C_6H_5CO^+$), 90 (100) ($C_6H_4N^+$).
IV.11	601 (26) (M^+), 524 (100) (M-C_6H_5), 498 (41) (M-C_6H_5-CH=CH), 105 (81.5) ($C_6H_5CO^+$), 90 (100) ($C_6H_4N^+$).

IR (IV.1-4): (KBr, cm^{-1}) 1680 cm^{-1} due to C=O stretching, 1610, 1580 and 1480 cm^{-1} are three bands of quinazoline ring system.

[2,4 (1H,3H)-Quinazolinedione-3-yl] acetic acid hydrazide (IX)

A mixture of the appropriate derivative of 3-Ethoxycarbonylmethyl-2,4-(1H,3H)- quinazolinediones (**VIII**) (0.01 mole and hydrazine hydrate (10 ml, 80%) in ethanol (10 ml) was stirred and heated at 50°C for two hours. The reaction mixture was cooled and treated with water (40 ml). The obtained crude product was collected by filtration, washed with water and then recrystallized from ethanol (**Table 7**).

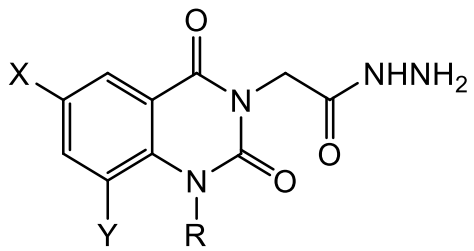


Figure 3 Chemical structure of compound IX

Table 7 [2,4 (1H,3H)-Quinazolinedione-3-yl] acetic acid hydrazide (IX)

Comp. IX	X	Y	R	Yield %	m.p. ˚C	M. Form./ M.Wt	Elemental analysis C	H	N
1	Br	Br	CH_3	100	230-2	$C_{11}H_{10}N_4O_3Br_2$	32.51	2.46	13.79
						406	32.68	2.61	13.82
2	Br	Br	C_2H_5	90	248-50	$C_{12}H_{12}N_4O_3Br_2$	34.28	2.85	13.33
						420	34.36	2.97	13.51
3	Br	Br	CH_2=CH-CH_2	95	261-3	$C_{13}H_{12}N_4O_3Br_2$	36.11	2.77	12.96
						432	36.23	2.76	12.96
4	Br	Br	*n*-C_3H_7	80	268-70	$C_{13}H_{14}N_4O_3Br_2$	35.94	3.22	12.90
						434	35.97	3.31	12.94
5	Br	Br	*n*-C_4H_9	80	274-6	$C_{14}H_{16}N_4O_3Br_2$	37.50	3.57	12.50
						448	37.67	3.63	12.71
6	Br	Br	C_6H_5	90	281-3	$C_{16}H_{12}N_4O_3Br_2$	41.02	2.56	11.96
						468	41.19	2.51	11.71
7	Br	Br	CH_2-C_6H_5	100	287-9	$C_{17}H_{14}N_4O_3Br_2$	42.32	2.90	11.61
						482	42.44	2.97	11.82
8	Br	Br	CO-C_6H_5	100	290-2	$C_{17}H_{12}N_4O_4Br_2$	41.12	2.41	11.29
						496	41.37	2.64	11.41
9	Br	Br	C_6H_{11}	75	295-7	$C_{16}H_{18}N_4O_3Br_2$	40.50	3.79	11.81
						474	40.67	3.91	11.88
10	Cl	Cl	CH_3	85	221-3	$C_{11}H_{10}N_4O_3Cl_2$	41.64	3.15	17.66
						317	41.81	3.34	17.83
11	Cl	Cl	C_2H_5	90	230-2	$C_{12}H_{12}N_4O_3Cl_2$	43.50	3.62	16.91
						331	43.78	3.76	16.98
12	Cl	Cl	CH_2=CH-CH_2	100	236-8	$C_{13}H_{12}N_4O_3Cl_2$	45.48	3.49	16.32
						343	45.70	3,62	16.51
13	Cl	Cl	*n*-C_3H_7	85	241-3	$C_{13}H_{14}N_4O_3Cl_2$	45.21	4.05	16.23
						345	45.34	4.22	16.31
14	Cl	Cl	*n*-C_4H_9	76.5	250-2	$C_{14}H_{16}N_4O_3Cl_2$	46.79	4.45	15.60
						359	46.93	4.52	15.60
15	Cl	Cl	C_6H_5	84	264-6	$C_{16}H_{12}N_4O_3Cl_2$	50.65	3.16	14.77
						379	50.87	3.31	14.90
16	Cl	Cl	CH_2-C_6H_5	76	267-9	$C_{17}H_{14}N_4O_3Cl_2$	51.90	3.56	14.24
						393	51.96	3.71	14.41
17	Cl	Cl	CO-C_6H_5	95	282-4	$C_{17}H_{12}N_4O_4Cl_2$	50.12	2.94	13.75
						407	50.37	2.98	13.94
18	Cl	Cl	C_6H_{11}	70	270-2	$C_{16}H_{18}N_4O_3Cl_2$	49.87	4.67	14.54
						385	49.96	4.76	14.61
19	I	H	CH_3	73	284-6	$C_{11}H_{11}N_4O_3I$	35.29	2.94	14.97
						374	35.41	2.96	14.98
20	I	H	C_2H_5	80	285-7	$C_{12}H_{13}N_4O_3I$	37.11	3.35	14.43
						388	37.35	3.57	14.60
21	I	H	CH_2=CH-CH_2	85	291-3	$C_{13}H_{13}N_4O_3I$	39.00	3.25	14.00
						400	39.07	3.46	14.13
22	I	H	*n*-C_3H_7	74.5	296-8	$C_{13}H_{15}N_4O_3I$	38.80	3.73	13.93
						402	38.61	3.92	13.80
23	I	H	*n*-C_4H_9	72	>300	$C_{14}H_{17}N_4O_3I$	40.38	4.08	13.46
						416	40.52	4.22	13.66
24	I	H	C_6H_5	80	>300	$C_{16}H_{13}N_4O_3I$	44.03	2.98	12.84
						436	44.18	3.04	12.91
25	I	H	CH_2-C_6H_5	83.6	>300	$C_{17}H_{15}N_4O_3I$	45.33	3.33	12.44
						450	45.50	3.41	12.64
26	I	H	CO-C_6H_5	85	>300	$C_{17}H_{13}N_4O_4I$	43.96	2.80	12.06
						464	43.82	2.66	12.20
27	I	H	C_6H_{11}	76.4	>300	$C_{16}H_{19}N_4O_3I$	43.43	4.29	12.66
						442	43.60	4.36	12.78

28	I	I	CH_3	70	>300	$C_{11}H_{10}N_4O_3I_2$	26.40	2.00	11.20
						500	26.51	2.11	11.34
29	I	I	C_2H_5	72	>300	$C_{12}H_{12}N_4O_3I_2$	28.01	2.33	10.89
						514	28.34	2.40	10.71
30	I	I	CH_2=CH-CH_2	80	>300	$C_{13}H_{12}N_4O_3I_2$	29.65	2.28	10.64
						526	29.81	2.40	10.79
31	I	I	*n*-C_3H_7	67	>300	$C_{13}H_{14}N_4O_3I_2$	29.54	2.65	10.60
						528	29.70	2.81	10.79
32	I	I	*n*-C_4H_9	65	>300	$C_{14}H_{16}N_4O_3I_2$	30.99	2.95	10.33
						542	31.12	3.01	10.50
33	I	I	C_6H_5	70	>300	$C_{16}H_{12}N_4O_3I_2$	34.16	2.13	9.96
						562	34.28	2.33	9.97
34	I	I	CH_2-C_6H_5	78	>300	$C_{17}H_{14}N_4O_3I_2$	35.41	2.43	9.72
						576	35.30	2.60	9.77
35	I	I	CO-C_6H_5	80	>300	$C_{17}H_{12}N_4O_4I_2$	34.57	2.03	9.49
						590	34.88	2.21	9.60
36	I	I	C_6H_{11}	64.5	>300	$C_{16}H_{18}N_4O_3I_2$	33.80	3.16	9.85
						568	33.93	3.25	9.87

2,3,4,6-Tetrahydro-2.5-dioxo-1H-1,2,4-triazino[4,3-c]quinazolines (X)

A mixture of the appropriate hydrazide (**IX**) (0.01 mole), fused sodium acetate (1 g.) and glacial acetic acid (30 ml) was refluxed for two hours. The obtained solid product was isolated and recrystallized from acetic acid to afford white crystalline solids (**Table 8**).

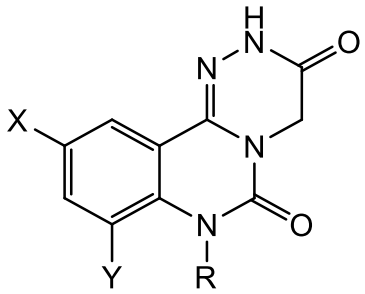


Figure 4 Chemical structure of compound X

Table 8 2,3,4,6-Tetrahydro-2.5-dioxo-1H-1,2,4-triazino[4,3-c]quinazolines (X)

Comp. X	X	Y	R	Yield %	m.p. ˚C	M. Form./ M.Wt	Elemental analysis C	H	N
1	Br	Br	CH_3	100	230-2	$C_{11}H_8N_4O_2Br_2$	34.02	2.06	14.43
						388	34.27	2.27	14.68
2	Br	Br	C_2H_5	90	248-50	$C_{12}H_{10}N_4O_2Br_2$	35.82	2.48	13.93
						402	35.95	2.67	13.84
3	Br	Br	CH_2=CH-CH_2	95	261-3	$C_{13}H_{10}N_4O_2Br_2$	37.68	2.41	13.52
						414	37.81	2.65	13.65
4	Br	Br	*n*-C_3H_7	80	268-70	$C_{13}H_{12}N_4O_2Br_2$	37.50	2.88	13.46
						416	37.71	2.95	13.57
5	Br	Br	*n*-C_4H_9	80	274-6	$C_{14}H_{14}N_4O_2Br_2$	39.06	3.25	13.02
						430	39.21	3.27	13.16
6	Br	Br	C_6H_5	90	281-3	$C_{16}H_{10}N_4O_2Br_2$	42.66	2.22	12.44
						450	42.81	2.40	12.45
7	Br	Br	CH_2-C_6H_5	100	287-9	$C_{17}H_{12}N_4O_2Br_2$	43.96	2.58	12.06
						464	43.99	2.69	12.19
8	Br	Br	CO-C_6H_5	100	290-2	$C_{17}H_{10}N_4O_3Br_2$	42.67	2.09	11.71
						478	42.81	2.23	11.95

9	Br	Br	C_6H_{11}	75	295-7	$C_{16}H_{16}N_4O_2Br_2$	42.10	3.50	12.28
						456	42.31	3.71	12.37
10	Cl	Cl	CH_3	85	221-3	$C_{11}H_8N_4O_2Cl_2$	44.14	2.67	18.72
						299	44.32	2.81	18.80
11	Cl	Cl	C_2H_5	90	230-2	$C_{12}H_{10}N_4O_2Cl_2$	46.00	3.19	17.89
						313	46.21	3.26	17.97
12	Cl	Cl	CH_2=CH-CH_2	100	236-8	$C_{13}H_{10}N_4O_2Cl_2$	48.00	3.07	17.23
						325	48.13	3,16	17.41
13	Cl	Cl	*n*-C_3H_7	85	241-3	$C_{13}H_{12}N_4O_2Cl_2$	47.70	3.66	17.12
						327	47.73	3.81	17.31
14	Cl	Cl	*n*-C_4H_9	76.5	250-2	$C_{14}H_{14}N_4O_2Cl_2$	49.26	4.10	16.42
						341	49.42	4.21	16.61
15	Cl	Cl	C_6H_5	84	264-6	$C_{16}H_{10}N_4O_2Cl_2$	53.18	2.77	15.51
						361	53.22	2.81	15.53
16	Cl	Cl	CH_2-C_6H_5	67	269-1	$C_{17}H_{12}N_4O_2Cl_2$	54.40	3.20	14,93
						375	54.62	3.43	14.97
17	Cl	Cl	CO-C_6H_5	95	282-4	$C_{17}H_{10}N_4O_3Cl_2$	52.44	2.57	14.39
						389	52.60	2.64	14.66
18	Cl	Cl	C_6H_{11}	70	270-2	$C_{16}H_{16}N_4O_2Cl_2$	52.31	4.35	15.25
						367	52.54	4.66	15.43
19	I	H	CH_3	73	284-6	$C_{11}H_9N_4O_2I$	37.07	2.52	15.73
						356	37.23	2.58	15.88
20	I	H	C_2H_5	80	285-7	$C_{12}H_{11}N_4O_2I$	38.91	2.97	15.13
						370	38.97	3.08	15.25
21	I	H	CH_2=CH-CH_2	85	291-3	$C_{13}H_{11}N_4O_2I$	40.83	2.87	14.65
						382	40.94	2.83	14.70
22	I	H	*n*-C_3H_7	74.5	296-8	$C_{13}H_{13}N_4O_2I$	40.62	3.38	14.58
						384	40.51	3.42	14.73
23	I	H	*n*-C_4H_9	72	>300	$C_{14}H_{15}N_4O_2I$	42.21	3.76	14.07
						398	42.44	3.91	14.19
24	I	H	C_6H_5	80	>300	$C_{16}H_{11}N_4O_2I$	45.93	2.63	13.39
						418	45.83	2.70	13.51
25	I	H	CH_2-C_6H_5	83.6	>300	$C_{17}H_{13}N_4O_2I$	47.22	3.00	12.96
						432	47.49	3.07	12.81
26	I	H	CO-C_6H_5	85	>300	$C_{17}H_{11}N_4O_3I$	45.73	2.46	12.55
						446	45.94	2.51	12.70
27	I	H	C_6H_{11}	76.4	>300	$C_{16}H_{17}N_4O_2I$	45.28	4.00	13.20
						424	45.29	4.11	13.34
28	I	I	CH_3	70	>300	$C_{11}H_8N_4O_2I_2$	27.41	1.67	11.62
						482	27.51	1.79	11.73
29	I	I	C_2H_5	72	>300	$C_{12}H_{10}N_4O_2I_2$	29.03	2.01	11.29
						496	29.31	2.19	11.40
30	I	I	CH_2=CH-CH_2	80	>300	$C_{13}H_{10}N_4O_2I_2$	30.70	1.96	11.02
						508	30.93	1.98	11.34
31	I	I	*n*-C_3H_7	67	>300	$C_{13}H_{12}N_4O_2I_2$	30.58	2.35	10.98
						510	30.62	2.44	10.99
32	I	I	*n*-C_4H_9	65	>300	$C_{14}H_{14}N_4O_2I_2$	32.06	2.67	10.68
						524	32.39	2.81	10.73
33	I	I	C_6H_5	70	>300	$C_{16}H_{10}N_4O_2I_2$	35.29	1.83	10.29
						544	35.41	1.97	10.43
34	I	I	CH_2-C_6H_5	78	>300	$C_{17}H_{12}N_4O_2I_2$	36.55	2.15	10.03
						558	36.74	2.49	10.21
35	I	I	CO-C_6H_5	80	>300	$C_{17}H_{10}N_4O_3I_2$	35.66	1.74	9.79
						572	35.90	1.89	9.95
36	I	I	C_6H_{11}	64.5	>300	$C_{16}H_{16}N_4O_2I_2$	34.90	2.90	10.18
						550	34.97	2.94	10.23

Table 9 ^{1}H NMR of 2,3,4,6-Tetrahydro-2.5-dioxo-1H-1,2,4-triazino[4,3-c]quinazolines (X)

Comp. X	δ, multiplicity, protons
X.1	10.40 (1H, s, NH-C=O-), 7.96 (1H, d, H-8), 7.89 (1H, d, H-10), 4.0 (2H, s, N-CH_2), 3.44 (3H, s, CH_3).
X.8	10.20 (1H, s, NH-C=O-), 8.03-7.63 (5H, m, aromatic H), 7.96 (1H, d, H-8), 7.89 (1H, d, H-10), 4.5 (2H, s, N-CH_2).
X.10	10.23 (1H, s, NH-C=O-), 7.77 (1H, d, H-10), 7.68 (1H, d, H-8), 4.05 (2H, s, N-CH_2), 3.44 (3H, s, CH_3).
X.19	10.20 (1H, s, NH-C=O-), 8.04 (1H, d, H-10), 7.66-7.63 (2H, m, H-8, H-7), 4.05 (2H, s, N-CH_2), 3.44 (3H, s, CH_3).
X.26	10.40 (1H, s, NH-C=O-), 8.04 (3H, m, aromatic H), 7.70-7.63 (5H, m, aromatic H), 4.05 (2H, s, N-CH_2),
X.30	10.21 (1H, s, NH-C=O-), 8.22 (1H, d, H-8), 8.03 (1H, d, H-10), 5.87 (1H, m, $\underline{CH}$=CH_2), 5.22 (2H, m, CH=$\underline{CH_2}$), 5.10 (2H, d, CH_2), 4.0 (2H, s, N-CH_2),

Table 10 Mass spectral data of compounds (X)

Comp. X	m/z (abound %)
X.1	387/389 (100/49) (M^+), 306 (42) (M-HBr), 282/284 (82.0/83.6) (M-C_6H_5CO), 168/170 (61.0/60.5) ($C_6H_3BrN^+$), 105 (100) ($C_6H_5CO^+$).
X.2	401/403 (100/51) (M^+), 320 (39) (M-HBr), 296/298 (75.0/76.4) (M-C_6H_5CO), 168/170 (61.0/60.5) ($C_6H_3BrN^+$), 105 (100) ($C_6H_5CO^+$).
X.10	298/300 (100/64) (M^+), 262 (37) (M-HCl), 193/195 (71.0/73.5) (M-C_6H_5CO), 174/176 (59.0/58.5) ($C_6H_3ClN^+$), 105 (100) ($C_6H_5CO^+$).
X.19	356 (100) (M^+), 105 (82.5) ($C_6H_5CO^+$), 90 (100) ($C_6H_4N^+$).
X.30	508 (100) (M^+), 467 (19.5) (M-CH_2-CH=CH_2), 437 (41) (M-$C_2H_3N_2O$), 380 (59) (M-$C_5H_8N_2O_2$), 370 (32) (M-$C_6H_8N_3O$), 328 (57) (M-$C_7H_8N_4O_2$), 105 (83.0) ($C_6H_5CO^+$), 90 (100) ($C_6H_4N^+$).

IR X): (KBr, cm^{-1}) 3200 cm^{-1} (NH stretching), 1700 cm^{-1} (C=O stretching) 1680, 1620, and 1490 cm^{-1} (quinazoline bands).

Pharmacological Tests

Adult albino mice of either sex weighing 20-25 gm. were used as experimental animals. Paracetamol (Sigma Chemical Co., St. Louis, MO, USA) and phenobarbitone sodium (Aldrich Chemical Co., St. Milwaukee, WI, USA) were used as reference drugs for analgesic and hypnotic actions. The test compounds as well Paracetamol were suspended in water by the aid of few drops of Tween-80 (Sigma) to produce 2% suspension. Phenobarbitone sodium was dissolved in water for injection containing a few drops of Tween-80 to produce 2% solution. *p*-benzoquinone (Aldrich) was dissolved in water for injection containing a few drops of Tween-80 to produce 0.02% solution and was used as writhing inducer.

A) Analgesic Action:

The analgesic action of some newly synthesized compound was determined using the writhing method on mice [34]. The mice were randomly arranged in groups each of 10 animals one group was kept as control. The animals of another group were given paracetamol subcutaneously in a dose of 30 mg/kg body weight. Mice of the other groups were blindly injected subcutaneously with test compounds in a dose of 150 mg/kg body weight. After 30 minutes, each animal of each group was injected with 0.25 ml of 0.02% aqueous solution of *p*-benzoquinone and was observed for writhing after 30, 60, 90, 120, and 180 minutes. Animals protected from writhing were recorded in each group and the analgesic potency of the test compounds was determined as percentage of protection against writhing. The results are presented in (**Table 11**).

Table 11 The analgesic effect of paracetamol and test compounds (III and X) in mice

Comp. No. III and X	Dose mg/kg	% of mice showing abolished writhing					
		Time (minutes)					
		30	60	90	120	150	180
Paracetamol (control)	20	100	100	100	100	100	100
III.1	150	80	80	80	80	80	80
III.2	150	90	90	90	90	90	90
III.3	150	90	90	90	90	90	90
III.4	150	80	80	80	80	80	80
III.5	150	90	90	90	90	90	90
III.6	150	90	90	90	90	90	90
X.1	150	100	100	100	100	100	100
X.2	150	100	100	100	100	100	100
X.3	150	100	100	100	100	100	100
X.4	150	100	100	100	100	100	100
X.5	150	100	100	100	100	100	100
X.6	150	100	100	100	100	100	100
X.7	150	100	100	100	100	100	100
X.8	150	100	100	100	100	100	100
X.9	150	100	100	100	100	100	100
X.10	150	100	100	100	100	100	100
X.11	150	100	100	100	100	100	100
X.12	150	100	100	100	100	100	100
X.13	150	100	100	100	100	100	100
X.14	150	100	100	100	100	100	100
X.15	150	100	100	100	100	100	100
X.16	150	100	100	100	100	100	100
X.17	150	100	100	100	100	100	100
X.18	150	100	100	100	100	100	100
X.19	150	100	100	100	100	100	100
X.20	150	100	100	100	100	100	100
X.21	150	100	100	100	100	100	100
X.22	150	100	100	100	100	100	100
X.23	150	100	100	100	100	100	100
X.24	150	100	100	100	100	100	100
X.25	150	100	100	100	100	100	100
X.26	150	100	100	100	100	100	100
X.27	150	100	100	100	100	100	100
X.28	150	100	100	100	100	100	100
X.29	150	100	100	100	100	100	100
X.30	150	100	100	100	100	100	100
X.31	150	100	100	100	100	100	100
X.32	150	100	100	100	100	100	100
X.33	150	100	100	100	100	100	100
X.34	150	100	100	100	100	100	100
X.35	150	100	100	100	100	100	100
X.36	150	100	100	100	100	100	100

B) Hypnotic Action:

The hypnotic action of some newly synthesized compound was determined by the loss of righting reflex on mice [35]. The animals were randomly arranged in groups each of six animals. Each of three graded doses of each test

compound as well as phenobarbitone was blindly injected subcutaneously to a group of animals. The animals were observed until loss of righting reflex and for further three hours later. The animal was considered asleep, during the time of loss of righting reflex till recovery. Mice showing hypnosis were counted in each group and the % hypnotic effect was calculated for each dose. The mean onset time, recovery time, % hypnotic effect ED_{50} and relative potency of test compounds to phenobarbitone are presented in (**Table 12**).

Table 12 Hypnotic Activity of Phenobarbitone (P) and Test Compounds (IV) in mice

Comp.	Dose mg/kg	No. of animals injected	No. of animals showing hypnosis	Mean onset time (minute), ± S.E	Recovery time (min.)	% Hypnotic effect	ED50 mg/kg	Relative potency
	100	6	3	25 ± 0.12	60	50		
IV.1	150	6	5	25 ± 0.32	90	84	100	1.49
	200	6	5	25 ± 0.42	90	100		
	100	6	4	15 ± 0.16	120	67		
IV.2	150	6	5	15 ± 0.23	120	84	65	2.87
	200	6	6	15 ± 0.44	120	100		
	100	6	4	15 ± 0.16	120	67		
IV.3	150	6	5	15 ± 0.23	120	84	65	2.87
	200	6	6	15 ± 0.44	120	100		
	100	6	2	10 ± 0.22	120	33		
IV.4	150	6	4	10 ± 0.32	120	67	64	3.07
	200	6	6	10 ± 0.12	120	100		
	100	6	4	20 ± 0.18	90	67		
IV.5	150	6	4	20 ± 0.23	120	67	77	2.56
	200	6	5	20 ± 0.47	120	84		
	100	6	3	45 ± 0.12	90	50		
IV.6	150	6	4	45 ± 0.32	90	67	100	1.95
	200	6	5	45 ± 1.5	120	84		
	100	6	3	30 ± 0.18	30	50		
IV.7	150	6	5	30 ± 0.25	60	84	100	1.65
	200	6	5	30 ± 0.27	90	84		
	100	6	3	35 ± 0.18	60	16		
IV.8	150	6	4	35 ± 0.32	90	67	139	1.00
	200	6	5	35 ± 0.42	90	84		
	100	6	1	35 ± 0.12	60	16		
IV.9	150	6	4	35 ± 0.36	60	67	139	1.00
	200	6	5	35 ± 0.58	90	84		
	100	6	4	20 ± 0.18	90	67		
IV.10	150	6	4	20 ± 0.23	120	67	77	2.56
	200	6	5	20 ± 0.47	120	84		
	100	6	3	25 ± 0.12	60	50		
IV.11	150	6	5	25 ± 0.32	90	84	100	1.49
	200	6	5	25 ± 0.42	90	100		
	100	6	3	45 ± 0.12	90	50		
IV.12	150	6	4	45 ± 0.32	90	67	100	1.95
	200	6	5	45 ± 1.5	120	84		
	100	6	1	40 ± 0.23	30	16		
IV.13	150	6	3	40 ± 0.28	30	50	150	1.02
	200	6	3	40 ± 0.49	30	50		
	100	6	4	20 ± 0.18	90	67		
IV.14	150	6	4	20 ± 0.23	120	67	77	2.56
	200	6	5	20 ± 0.47	120	84		
	100	6	2	10 ± 0.22	120	33		
IV.15	150	6	4	10 ± 0.32	120	67	64	3.07
	200	6	6	10 ± 0.12	120	100		
IV.16	100	6	1	15 ± 0.23	90	16	70	2.26

	150	6	4	15 ± 0.18	120	67		
	200	6	6	15 ± 0.12	180	100		
	100	6	1	35 ± 0.12	60	16		
IV.17	150	6	4	35 ± 0.36	60	67	139	1.00
	200	6	5	35 ± 0.58	90	84		
	100	6	3	30 ± 0.18	30	50		
IV.18	150	6	5	30 ± 0.25	60	84	100	1.65
	200	6	5	30 ± 0.27	90	84		
	50	6	1	25 ± 0.48	40	16		
P	100	6	3	25 ± 0.27	60	50	100	1.00
	150	6	6	25 ± 0.35	90	100		

Results and Discussion

Many substituted 4H-3,1-benzoxazin-4-ones (**II**) were obtained by refluxing the appropriate anthranilic acid (**I**) with acetic and propionic anhydrides. Condensation of the different benzoxazinones (**II**) with anthranilamide in refluxing glacial acetic acid containing small quantity of fused sodium acetate afforded the new quinazolinoquinazolinones (**III**) (**Table 1**). The structures of such new compounds were confirmed by both elemental and spectral analyses. The IR spectra of (**III**) in KBr showed carbonyl stretching around 1690-1700 cm^{-1} and the three indicative bands of the quinazoline ring system at 1600, 1560 and 1480 cm^{-1}. The ^1H NMR spectra of (**III**) in DMSO-d_6, taking (**III.3**) as a model example, showed two fine doublets each of one proton, at 8.24 and 8.05 ppm (H-9 and H-11 respectively), two course doublets each of one proton at 7.64 and 7.31 ppm, (H-1 and H-4 respectively), and two triplets each of one proton at 7.76 and 7.00 ppm (H-3 and H-2 respectively). The methyl group at position-6 revealed as sharp singlet of three protons at 2.12 ppm. The EI mass spectra of (**III**) are characterized by the presence of prominent molecular ion peaks representing the base peaks in some cases. Loss of the C-6 substituent, CN, CO, and R-CN were the most common fragmentation processes of such compound. The 6- methyl derivatives of (**III**) were allowed to react with certain aldehydes, namely acetaldehyde, benzaldehyde, 2-chlorobenzaldehyde, 4-chlorobenzaldehyde, 2,4-dichloro-benzaldehyde, 2,6-dichlorobenzaldehyde, 4-methoxybenzaldehyde, 2,4-dimethoxybenz-aldehyde, 4-hydroxybenzaldehyde whereby, the corresponding 6-vinyl derivatives (**IV**) were obtained (**Table 4**). The structures of (**IV**) were confirmed by both elemental and spectral analyses. The IR spectra of (**IV**) in KBr showed the carbonyl stretching at 1680 cm^{-1} in addition to the other double bond stretching at 1610, 1580, 1560, 1500, and 1480 cm^{-1}. The ^1H NMR spectra of (**IV**) in DMSO-d_6, e.g. (**IV.4**) is characterized by the presence of two doublets each of one proton at 7.10 and 6.50 ppm due to vinyl protons. The rest aromatic protons revealed multiplet in the region of 8.20-7.0 ppm. Also the ^1H NMR spectrum of compound (**IV-2)** is characterized by the presence of two doublets at 8.10 ppm and 7.20 ppm, (vinyl protons). The aromatic protons appear as multiplet in the region of 8.06-7.0 ppm. The EI mass spectra of (**IV**) showed the molecular ion peaks. The base peaks were produced in most cases by loss of the 6-vinyl moiety. Loss of CO, CN and C_6H_4 were also observed. In addition, alkylation of certain anthranilic acids (**I**) with various alkyl halides in the presence of sodium carbonate afforded several N-alkylanthranilic acids (**V**) which were fused with urea to produce the corresponding 2,4(1H,3H)-quinazolinediones (**VI**). Treatment of (**VI**) with KOH in absolute ethanol yielded the respective potassium salts (**VII**) which on heating with ethyl chloroacetate in DMF produce the corresponding esters (**VIII**). Hydrazinolysis of (**VIII**) gave the hydrazides (**IX**). The structures of the hydrazides were confirmed by elemental and spectral analyses. The IR spectra of (**IX**) in KBr showed strong absorption band near 3200 cm^{-1}, due to NH stretching, and two sharp strong bands at 1710 and 1665 cm^{-1}, due to C-4 carbonyl, amide- I-band and C-2 carbonyl streatchings. The amide –II- band as well as skeletal vibrations of quinazoline nucleus revealed absorption bands at 1610, 1550, and 1485 cm^{-1}. Refluxing hydrazides (**IX**) in glacial acetic acid containing fused sodium acetate afforded the new 1,2,4-triazino[4,3-c]quinazolines (**X**). The reaction was observed to proceed via an intramolecular cyclodehydration. It is well known that the C-4 of the quinazoline ring system is more electrophilic than the C-2 which is flanked by two nitrogens [36]. This difference in electrophilicity between these two carbons may explain the preferential attack of the terminal nitrogen of the hydrazide moiety on the C-4 to yield compounds (**X**). The structures of (**X**) were confirmed by elemental and spectral analyses. The IR spectra of (**X**) in KBr showed strong bands at 3200 cm-1 (NH stretching), at 1700 cm-1 (C=O stretching) and at 1680, 1620, and 1490 cm^{-1} (quinazoline bands). The ^1H NMR spectra of (X) in DMSO d-6, taking (**X.1**) as a model example revealed a downfield singlet of one proton at 10.40 ppm (NH-C=O), singlet of two proton at 4.0 ppm (-CH_2 protons of triazino ring), singlet of three protons at 3.44 ppm due to (CH_3 protons). The aromatic protons of the fused benzene

ring displayed two doublets each of one proton at 7.96, 7.89 ppm (H-8 and H-10 respectively). The EI mass spectra of (**X**) showed molecular ion peaks in most cases. Loss of the 6-substituent is common feature in this series. A preliminary, double-blind and randomized study was undertaken to evaluate the non-narcotic analgesic activity of (**III**) and (**X**) using paracetamol as reference drug the hypnotic action of (**IV**) using phenobarbitone as a reference compound. Loss of righting reflex was taken as a parameter for evaluation of the hypnotic activity of the test compounds; while protection of the experimental animals against p-benzoquinone induced writhing was adopted for estimation of the analgesic activity of such compounds. The results presented in (**Table 11**) revealed that some triazinoquinazolines (i.e. **X.1-32**) showed an appreciable analgesic activity compared with paracetamol. These derivatives exhibited 100% protection against p-benzoquinone induced writhing in mice at dose level of 150 mg/kg. The other quinazolinoquinazolines (**III**) showed much less analgesic effect. On the other hand, the results presented in (**Table 12**) revealed that compounds (**IV**) possess a marked hypnotic activity compared with phenobarbitone. The ED50 of phenobarbitone was 100 mg/kg and its onset time was 25 minutes. Careful inspection of data (**Table 12**) showed that compounds (**IV.8, IV.9** and **IV.17**) exhibited a hypnotic action similar to that of phenobarbitone. The other compounds are more active than phenobarbitone Introduction of Iodine at position 10 and 8 greatly increased the potency, significantly decreased the onset time and considerably increased the duration of action. Replacing the CH_3 group of the vinyl moiety by a phenyl or 2-chlorophenyl group, 4-chlorophenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 4-methoxyphenyl, slightly increased both onset time and potency.

Computational drug design:

1. Analgesic anti-inflammatory:

Docking studies were carried out to examine the analgesic and anti-inflammatory effect of compounds (**III.1-6** and **X.1-36**).

Preparation of the target protein:

The protein target needs to be prepared and modeled according to the format requirements of the docking algorithms used. Thus the required protein was downloaded from protein data bank (PDB) (code 1RO6) using Discovery Studio 2.5 software. Water molecules were removed from downloaded protein. Crystallographic disorders and unfilled valence atoms were corrected using alternate conformations and valence monitor options. Protein was subjected to energy minimization by applying CHARMM force fields for charge, and MMFF94 force field for partial charge. Inflexibility of structure is obtained by creating fixed atom constraint. The binding site of the protein was defined and prepared for docking.

Tested compounds preparation:

The designed compounds 2D structures were sketched using ChemBioDraw Ultra 14.0 and saved in MDL-SDfile format. SDfile opened, 3D structures were protonated and energy minimized by applying CHARMM force fields for charge, and MMFF94 force field for partial charge, then prepared for docking by optimization of the parameters.

Results and Discussion:

The obtained results indicated that all studied ligands have similar position and orientation inside the putative binding site of the phosphodiesterase4 protein. The selected compounds (**X.35, X.36** and **X.27**) showed good binding energies ranging from – 40 to - 42.11 kcal/mol. The proposed binding mode of compound (**X.35**) (affinity value of – 40 kcal/mol and 2 H-bonds) is shown in (**Figure 5**). One carbonyl group formed a hydrogen bond with a distance of 1.87 A˚ with Asn395. The basic nitrogen of the ring formed a further hydrogen bond with a distance of 2.09 A˚ with the acidic proton of Gln443. Furthermore, the compound formed a Pi-Pi interaction with Phe446 and a Pi-sigma interaction with Ile410. The proposed binding mode of compound (**X.36**) (affinity value of – 42.08 kcal/mol and 3 H-bonds) is shown in (**Figure 6**). One carbonyl group formed a hydrogen bond with a distance of 1.95 A˚ with Asn395. The basic nitrogen of the ring formed a further hydrogen bond with a distance of 2.05 A˚ with the acidic proton of Gln443 and the amidic proton formed a hydrogen bond with a distance of 2.40 A˚ with Gln443. Furthermore, the compound formed a Pi-Pi interaction with Phe446 and a Pi-sigma interaction with Ile410. The proposed binding mode of compound (**X.27**) (affinity value of – 42.11 kcal/mol and 3 H-bonds) is shown in (**Figure 7**). One carbonyl group formed a hydrogen bond with a distance of 1.98 A˚ with Asn395. The basic nitrogen of the ring formed a further hydrogen bond with a distance of 2.04 A˚ with the acidic proton of Gln443 and the amidic proton formed a hydrogen bond with a distance of 2.41 A˚ with Gln443. Furthermore, the compound formed a Pi-Pi interaction with Phe446 and a Pi-sigma interaction with Ile410

Table 13 ΔG for ligands III.1-6 and X.1-36

Comp.	ΔG	Comp.	ΔG	Comp.	ΔG
III.1	-23.43	**X.9**	-26.55	**X.23**	-23.33
III.2	-31.07	**X.10**	-24.44	**X.24**	-27.22
III.3	-22.23	**X.11**	-35.18	**X.25**	-22.96
III.4	-28.54	**X.12**	-22.09	**X.26**	-30.10
III.5	-21.22	**X.13**	-25.65	**X.27**	-42.11
III.6	-30.04	**X.14**	-31.33	**X.28**	-39.43
X.1	-31.17	**X.15**	-30.09	**X.29**	-29.00
X.2	-30.32	**X.16**	-24.09	**X.30**	-23.45
X.3	-22.56	**X.17**	-30.00	**X.31**	-39.10
X.4	-21.22	**X.18**	-25.43	**X.32**	-28.98
X.5	-33.47	**X.19**	-22.23	**X.33**	-31.48
X.6	-34.48	**X.20**	-32.11	**X.34**	-33.05
X.7	-31.33	**X.21**	-26.39	**X35**	-40.00
X.8	-27.54	**X.22**	-26.39	**X36**	-42.08

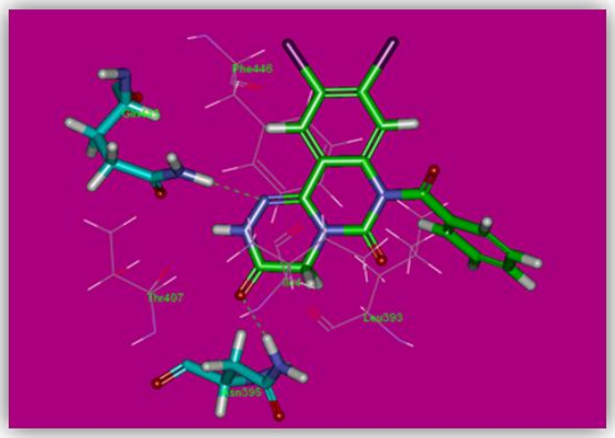


Figure 5 Binding mode of compound X.35

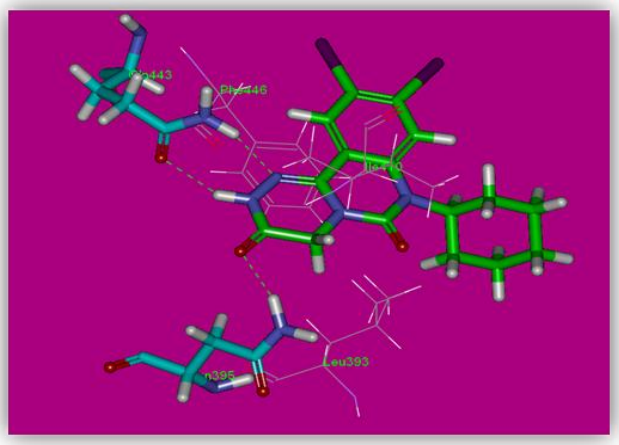


Figure 6 Binding mode of compound X.36

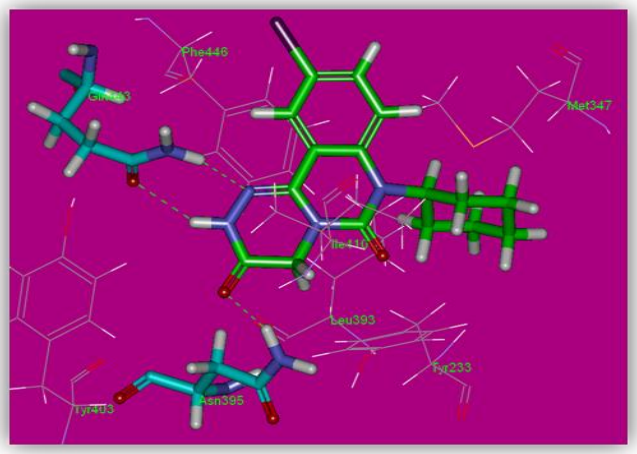


Figure 7 Binding mode of compound X.27

2. Sedative Hypnotic:

Docking studies were carried out to examine the effect of compounds (**IV.1-18**) on the GABA-A receptor.

Preparation of the target protein:

The protein target needs to be prepared and modeled according to the format requirements of the docking algorithms used. Thus the required protein was downloaded from protein data bank (PDB) (code 4COF) using Discovery Studio 2.5 software.

Table 14 ΔG for ligands IV.1-18

Comp.	ΔG	Comp.	ΔG	Comp.	ΔG
IV.1	-22.05	**IV.7**	-21.34	**IV.13**	-22.07
IV.2	-22.29	**IV.8**	-23.30	**IV.14**	-22.05
IV.3	-27.01	**IV.9**	-23.18	**IV.15**	-18.20
IV.4	-25.24	**IV.10**	-21.98	**IV.16**	-28.20
IV.5	-20.22	**IV.11**	-20.03	**IV.17**	-27.61
IV.6	-21.11	**IV.12**	-25.18	**IV.18**	-21.12

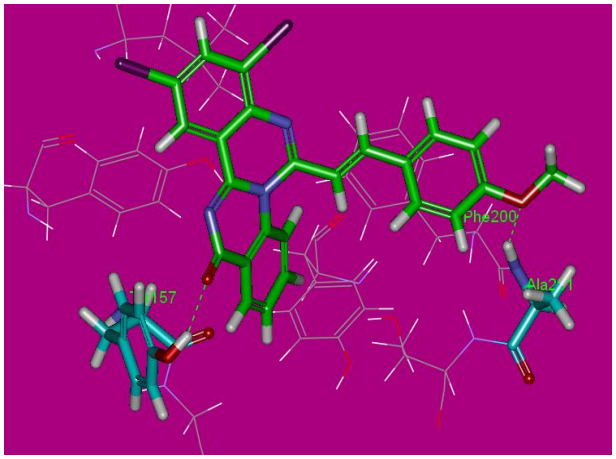


Figure 8: Binding mode of compound IV.16

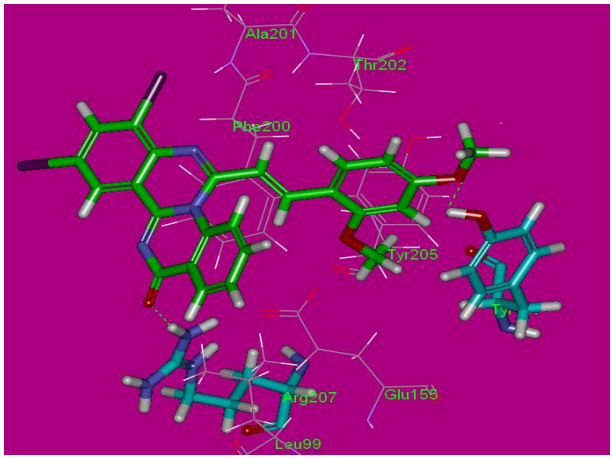


Figure 9 Binding mode of compound IV.17

Results and Discussion:

The obtained results indicated that all studied ligands have similar position and orientation inside the putative binding site of GABA-A receptor. The selected compounds (**IV.16** and **IV.17**) showed good binding energies ranging from – 28.20 to -27.61 kcal/mol. The proposed binding mode of compound (**IV.16**) (affinity value of – 28.20 kcal/mol and 2 H-bonds) is shown in (**Figure 8**). One carbonyl group formed a hydrogen bond with a distance of 2.01 A˚ with Tyr157. The O atom of the methoxy group formed a further hydrogen bond with a distance of 2.31 A˚ with the acidic proton of Aln201. Furthermore, the compound formed a Pi-Pi interaction with Phe200. The proposed binding mode of compound (**IV.17**) (affinity value of – 27.61 kcal/mol and 2 H-bonds) is shown in (**Figure 9**). One carbonyl group formed a hydrogen bond with a distance of 2.21 A˚ with Arg207. The O atom of the methoxy group formed a further hydrogen bond with a distance of 2.22 A˚ with the acidic proton of Tyr157. Furthermore, the compound formed a Pi-Pi interaction with Phe200.

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