Regular Article

Synthesis of some safe anticonvulsant quinazolinone and pteridinone-yl-2-oxothio/barbituric acid derivatives

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According to this study, five compounds (methyl–3,1-benzoxazin-4-one (I), 2,2'-dimethyl-[3,3'] biquinazolinyl-4,4'-dione (III), 5-[(2-mercapto-4-oxoquinazolin-3 (4H)-ylamino) methyl]-2-thiobarbituric acid (IX), isopropyl-3-[(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1h-pyrazol-4-yl) methylamino]-4-oxo-3Hquinazoline 2 (XII) and 5-[(2-isopropyl-4-oxoquinazolin-3 (4H)-ylamino) methyl)-2-thiobarbituric acid (XIII)) were found to be significantly active and safe anticonvulsant in mice. Compounds III were obtained during the reaction of compound I with hydrazine hydrate. On applying mannich reaction to VII, compound IX was produced. Compounds XII, XIII were synthesized by applying the same reaction on 2-isopropyl quinazolinone with thiobrbituric acid on microwave.

Key words:

Anticonvulsant, epilepsy, pteridinone, quinazoline

Epilepsy is one of the most common neurological disorders. It affects about 1% of the world's population. Research efforts led to the development of several new agents as promising anticonvulsants. However, these agents suffer from several side effects (Maggio *et al*., 2001).

Quinazolinone derivatives have been reported to be biologically versatile compounds possessing variety of activity including anticonvulsant property. In 1999, Santagati *et al*., synthesized methaqualone as a sedative hypnotic, which consequently represented an important landmark in the field of synthetic anticonvulsant (Hazarkhani and Karimi (2003), Weber *et al*., (2003), Liu *et al*., (2005, 2006), Archana *et al*., (2004), Watkins *et al*., (2007) and Connolly *et al*., (2005)). However, pteridinone exhibited several pharmacological actions (Grover *et al*., 2005), anti-histaminic (Zhang *et al*., 2007), anti-allergic (Kamal *et al*., 2006) and anti-hypertensive (de *et al*., 2005). In view of the above considerations and aiming to locate novel anticonvulsants, we reported the synthesis of the title compounds in which the two moieties were joined in one molecule by applying Mannich reaction on the active methylene. Remarkable anticonvulsant properties were observed by most of the tested compounds.

Experimental Protocol

Chemistry

Melting points were recorded in open capillaries on Gallenkamp hot stage or Reichert Hot stage microscope and were uncorrected. Infrared (IR) spectra were measured with Perkin–Elmer, FT-IR Spectrometer, using potassium bromide and results are given as per centimetre (/cm). NMR spectra were recorded in $CDCl_3$, CD_3OD, DMSO-d_6 on JEOL-NMR 400 MHz spectrometer. The chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Electron impact MS spectra were obtained on MAT-711 spectrometer, inlet temp 200, ionization energy 70 eV. Mass spectra were run on Hewlett Packard 5988 spectrometer, some reactions under microwave irradiation model Galanz Microwave Oven WP 1000AL23. The progress of all reactions was monitored by TLC on TLC sheet, silica gel 60 F_{254} layer thickness 0.2 mm (5 × 10 cm) and TLC plates pre-coated silica gel 60 (20 × 20 cm). The developed chromatograms were viewed under ultraviolet light. Column chromatography was performed on silica gel 0.13-0.25 mm (60-120) mesh and Sephadex LH- 20 μm (25-100).

2-Methyl–3, 1-benzoxazin-4-one (I)

Method (1)

Acetic anhydride (50 ml) was heated (100-110°C) and anthranilic acid (4.11 g, 0.03 mol) was added. The mixture was refluxed for 25 min and then evaporated under reduced pressure. The residue was cooled. The product was filtered off, washed with petroleum ether (40–60°C) and purified by crystallization

from acetic anhydride. The physical property is shown in Table 1.

Method (2)

A mixture of anthranilic acid (4.11 g, 0.03 mol) and acetic anhydride (0.1 mol) was irradiated at power input (60 W), the reaction was monitored by TLC till completion. The product was washed with petroleum ether (40–60°C). The physical data are shown in Table 1.

3-Amino-2-methyl–3H-quinazolin-4-one (II)

2-Methyl-3,1-benzoxazin-4-one (I) (1.61 g, 0.01mol), hydrazine hydrate 99% (0.01 mol) ware heated under reflux in EtOH (30 ml) (4 h) until completion TLC monitoring ($CHCl_3$:EtOH) (7:3). The reaction mixture was filtered while hot and the product compounds (II) (III) and (IV) were isolated by (TLC). The physical and spectral data are shown in Tables 1-4.

3-(4-Aminophenyl)-2-methyl-3H-quinazolin-4-one (V)

Method (1)

2-Methyl-3,1-benzoxazin-4-one (I) (1.61 g, 0.1 mol) and *p*-phenylenediamine (1.08 g, 0.1 mol) were heated under reflux in dry pyridine for 8 h. The reaction was cooled and treated with acidic ice water (10% hydrochloric acid). The separated solid was washed with water and then crystallized from ethanol.

Method (2)

2-Methyl-3,1-benzoxazin-4-one (I) (1.61 g, 0.1 mol), *p*-phenylenediamine (1.08 g, 0.1 mol) and acetic acid (50 ml) were heated under reflux in oil bath for 4 h. The reaction mixture was filtered and re-crystallized from ethanol.

Method (3)

A mixture of anthranilic acid (1.37 g, 0.1 mol) *p*-phenylenediamine (1.08 g, 0.1 mol) acetic anhydride (1.05 ml) was irradiated at power input (600 W) for (6 min). The physical and spectral data are shown in Tables 1-4.

Table 1: Physical properties of compounds (I-XXI)

Compound no.	Molecular formula	M.p (°C)	Yield (%)	Color and shape of crystals
I	$C_9H_7NO_2$	79	71[a],78[b]	White slides
II	$C_9H_9N_3O$	270	63	Ruph slides
III	$C_{18}H_{14}N_4O_2$	160	65	Red needles
IV	$C_{16}H_{14}N_4O_2$	110	12	Ruph needles
V	$C_{15}H_{13}N_3O$	161	50[a],73[b],80[c]	Green needles
VI	$C_{26}H_{23}N_5O_2$	320	32	Brown needles
VII	$C_8H_7N_3OS$	200	19	Yellow needles
VIII	$C_{16}H_{14}N_6O_2S_2$	300	82	White needles
IX	$C_{13}H_{11}N_5O_3S_2$	250	17	Orange needles
XI	$C_{16}H_{17}N_5O_4$	238	55	Yellow needles
XII	$C_{16}H_{17}N_5O_3S$	200	84	White slides
XIII	$C_{22}H_{23}N_5O_2$	200	76	Brown needles
XIV	$C_{20}H_{25}N_3O_3$	150	58	Ruph slide
XV	$C_{19}H_{17}NO_5$	200	40	Orange needles
XVIa	$C_{27}H_{24}N_2O_6$	195	40[a],61[b]	Yellow needles
XVIb	$C_{27}H_{23}BrN_2O_6$	320	17[a],62.95[b]	Brown needles
XVIII	$C_7H_5N_3O_2$	110	72	White slides
XIX	$C_{13}H_{11}N_5O$	200	30	Brown needles
XX	$C_7H_7N_3O_3$	123	10	Ruph needles
XXI	$C_{22}H_{23}N_5O_3$	180	20	Brown needles

a = Method (1); b = Method (2); c = Method (3)

2-Methyl-3-{4-[(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-ylmethyl)-amino]-phenyl}-3H-quinazolin-4-one (VI)

A solution of 3-methyl-1-phenyl-pyrazol-5-one (1.74 g, 0.01 mol), compound V and formaldehyde (0.02 mol) in EtOH (60 ml) was refluxed for 11 h, and then evaporated under reduced pressure. The product was filtered off, washed with *n*-hexane and purified after separation by column chromatography ($CHCl_3$: EtOH) (9:1). The physical and spectral data are shown in Tables 1-4.

3-Amino-2-mercapto- 3H- quinazolin-4-one (VII)

To a vigorously stirred solution of methyl anthranilate (1.51 g, 0.02 mol) in dimethylsolfoxide (10 ml) at room temperature, carbon disulphide (1.6 ml) and aqueous sodium hydroxide (1.2 ml) was added drop wise with stirring for 1 h. Dimethyl sulphate (0.02 mol) was added drop wise with cooling in an ice bath. Stirring was continued for 3 h, the reaction mixture was poured into ice-water and then extracted with chloroform. The solvent was removed by distillation under reduced pressure. The obtained dithiocarbamate was used without purification. Hydrazine hydrate (0.2 mol) was added drop wise to stirred dithiocarbamate (0.02 mol) in cold condition. After adding, stirring was continued for 2 h at 50°C and the mixture was poured into ice-water. The solid obtained was filtered, washed with water, dried and purified by column chromatography (EtOH: *n*-Hexane: $CHCl_3$) (4:3:3). The physical and spectral data are shown in Tables 1 and 2.

5-[(2-Mercapto-4-oxoquinazolin-3 (4H)-ylamino) methyl]-2-thiobarbituric acid (IX)

To a solution of thiobarbituric acid (1.44 g, 0.1 mol) in ethanol, compound VII and formaldehyde (0.02 mol) in ethanol (60 ml) was added. The reaction mixture was refluxed for 7 h then evaporated under reduced pressure. The product was filtered off, washed with methanol and purified after separation by (TLC) (EtOH: *n*-Hexane: $CHCl_3$) (4:3:3). The physical and spectral data are shown in Tables 1 and 2.

5-[(2-Isopropyl-4-oxoquinazolin-3 (4H)-ylamino) methyl]-barbituric acid (XI)

A mixture of 3-amino-2-isopropyl-4-oxoquinazoline (X) (1 mmol), barbituric acid (1 mmol), formaldehyde (3 mmol) and acetic acid (1 mol) was irradiated for 5 min in a microwave oven at medium power. After cooling, the reaction mixture was poured onto crushed ice (40 g) and stirred for 5–10 min. The separated solid was filtered, washed with water dried and crystallized. The physical and spectral data are shown in Tables 1 and 4.

2-Isopropyl-3-[(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl) methylamino]- 4-oxo-3Hquinazoline 2 (XII)

A mixture of compound (X) (1 mol), 3-methyl-1-phenylpyrazol-5-one (1 mol) formaldehyde (3 mol) and acetic acid (1 mol) was irradiated in a microwave oven at medium power. After cooling, the separated solid was filtered washed with water and purified by column chromatography ($CHCl_3$: Benzene: EtOH) (7:2:1). Physical and spectral data are shown in Tables 1 and 4.

Table 2: ^{1}H-NMR spectra data of compounds (II-IX)

Compound δ (ppm) of ^{1}H (*J*) Hz	II	III	IV	V	VI	VII	VIII	IX
H-5	8.06, (d, J_3=7.34 Hz)	7.87 (1H, dd, ^3J=7.89, ^4J=1.28)	6.70 (1H, d, ^3J=8.07)	8.47 (1H, d, ^3J=8.44)	7.78 (3H, d, ^3J=8.07, H, C-5,2',6')	7.90 (2H, m, H_5, H_7)	7.44 (1H, d, ^3J=8.07)	4.18 (1H, d)
H-6	7.70 (t, ^3J=7.34 Hz)	7.27 (1H, t, ^3J=7.52)	7.16 (1H, t, ^3J=7.71)	7.13 (1H, t, ^3J=7.52)	7.14 (2H, t, ^3J=6.79)	7.08 (1H, m, H, C-6)	7.26 (1H, t, ^3J=7.34)	
H-7	7.79 (t, 7.34H)	7.97 (1H, td, ^3J=7.70, ^4J=1.47)	6.47 (1H, t, ^3J=7.52)	7.54 (1H, t, ^3J=7.70)		7.90 (2H, H, C-5 and C-7)	7.26 (1H, t, ^3J=7.34)	8.36 (1H, d, ^3J=8.44)
H-8	7.50, (d, J_3=7.34 Hz)	7.79 (1H, d, ^3J=8.07)	7.71 (1H, d, ^3J=7.70)	7.97 (1H, d, ^3J=8.07)		7.17 (3H, m, H, C-8 and NH_2)	7.09 (1H, t ,^3J=7.52)	
CH_3	2.02 (5H, s)	2.60 (3H, s)		2.6 (3H, s)				
H-5'		8.36 (1H, d, ^3J=8.44)	8.10 (1H, d, ^3J=7.71)				9.02 (1H, d, ^3J=8.44)	8.23 (1H, d, ^3J=7.71)
H-6'		7.58 (1H, dd, ^3J=7.70 ^4J=1.47)	7.47 (1H, t, ^3J=7.52)		7.78 (3H, d, ^3J=8.07, H, C-5, 2', 6')		7.54 (1H, t, ^3J=7.89)	7.72-7.56 (5H, m, 3NH, H6', H7')
H-7'		7.63 (1H, t, ^3J=7.89)	7.76 (1H, t, ^3J=7.52)				7.65 (1H, t, ^3J=6.97)	
H-8'		8.18 (H, d, ^3J=6.97)	7.59 (1H, d, ^3J=8.07)				8.00 (1H, d, ^3J=6.97)	7.37 (1H, d, ^3J=9.18)
CH_3'		2.16 (3H, s)	2.58 (3H, s)		1.91 (6H, s, 2 CH_3)			
NH, NH_2	2.02 (5H, s)		5.97 (3H, s, br)	7.19 (2H, s)	7.19 (2H, s)	5.49 (1H, s)	11.93 (1H, s) 5.66 (2H, s) 9.99 (1H, s)	7.72-7.56 (5H, m, NH, H_6', H_7')
C-2' and C-6'			7.23 (2H, d, ^3J=7.5)	7.23 (2H, d ,^3J=7.5)	7.78 (3H, d, ^3J=8.07, H, C-5, 2', 6')			
C-3' and C-5'			7.07 (2H, d, ^3J=7.70)	7.07 (2H, d, ^3J=7.70)	6.70 (3H, d, ^3J=8.07 H, C-8, 5', 3',)			
C-2" and C-6"'					7.93 (2H, d, ^3J=6.61)			
C-3"' and C-5"'					6.58 (3H, t, ^3J=6.60, H, C-5"', 4"', 3"')			
C-4"'					1.91 (6H, s, 2CH_3)			
CH_2					2.70-2.35 (3H, CH_2, H, C-4")	3.74, 0.69 (H_a, H_b)		
SH						7.69 (1H, s)	4.59 (2H, s)	6.13 (1H, s)

5-[(2-Isopropyl-4-oxoquinazolin-3 (4H)-ylamino) methyl)-2-thiobarbituric acid (XIII)

A mixture of 3-amino-2-isopropyl-4oxo-3*H*-quinazoline (X) (1 mmol), thiobarbituric acid (1 mmol), formaldehyde (3 mmol) and acetic acid (1 mmol) was irradiated in a microwave oven of medium power for 1 min. After cooling, the separated solid was filtered washed with water and dried. The physical and spectral data are shown in Tables 1 and 4.

2-[(2-Isopropyl-4-oxoquinazolin-3 (4H)-ylamino) methyl]-4,4-dimethylcyclohexane-1,3-dione (XIV)

A mixture of compound (**X**) (1 mol), 4,4-dimethylcyclohexane-1,3-dione (1 mol), formaldehyde (3 mol) and acetic acid (1 mol) was irradiated for 4 min and 30 s in a microwave oven at medium power. After cooling, the separated solid was filtered, washed with water and crystallized from ethanol. Physical and spectral data are shown in Tables 1 and 4.

2-Phenyl-4- (2,4,5-trimethoxy-benzylidene)- 4H-oxazol-5-one (XV)

A mixture of benzoylglycine (0.01 mol), 2,4,5-trimethoxybenzaldehyde (0.01 mol) and sodium acetate (0.006 mol) in acetic anhydride (20 ml) was heated in a boiling water bath for 8 h., the crystalline product obtained on cooling was filtered, washed with water and crystallized from acetic acid. Physical and spectral data are shown in Tables 1, 5 and 6.

Methyl 2-(5-oxo-2-phenyl-4- (2,4,5-trimethoxybenzylidene)-4,5-dihydroimidazol-1-yl) benzoate. (XVIa)

Method 1

2-Phenyl-4-(2,4,5- trimeth oxy- benzyli dene)-4H-oxaz ol-5-one (XV) (0.01 mol) and methyl anthranilate (0.01 mol) were fused in dry condition for 3 h then washed with EtOH, filtered, then purified by column chromatography. The physical and spectral data are shown in Tables 1, 5 and 6.

Table 3: ^{13}C-NMR spectral data of compounds (II-IX)

Compound carbon. no.	II	III	IV	V	VI	VII	VIII	IX
C-2	151.04	159.00	170.75	169.02	163.42	153.15	121.14	175.07
C-4	166.35	169.22	112.21	170.03	168.61	168.00	148.41	171.14
C-4a	130.00	112.59	151.78	117.00	128.31	115.83	125.81	52.54
C-5	132.02	128.62	116.65	131.61	128.56	130.59	134.76	171.14
C-6	130.15	121.82	126.48	120.18	116.54	126.78	120.85	-
C-7	134.16	132.93	114.94	134.55	128.56	134.27	131.99	-
C-8	130.84	124.33	126.48	120.49	127.70	128.78	166.00	-
C-8a	130.84	137.81	-	143.96	142.08	150.67	160.31	-
CH_3-C_2-	11.11	25.21	-	25.55	29.33		121.14*	-
C-2'	-	154.42	156.11	-	138.75	187.93	161.64	153.69
C-4'	-	163.87	160.63	-	131.34	173.39	167.84	168.45
C-4a'	-	120.73	120.30	-	129.00	114.51	123.64	115.19
C-5'	-	128.18	133.51	-	138.97	124.46	128.27	130.21
C-6'	-	127.47	127.17	-	148.06	121.64	122.17	126.16
C-7'	-	136.65	134.48	-	67.61	135.74	139.18	134.64
C-8'	-	127.95	131.83	-	173.61	123.13	126.63	127.71
C-8a'	-	147.01	147.15	-	140.26	140.21	147.87	135.59
(CH_3)-C-2'	-	11.09	22.47	-	132.06	-	-	-
C-1'	-	-	-	123.10		-	-	-
C-2' and C-6'	-	-	-	129.69	115.84	-	-	-
C-3' and C-5'	-	-	-	117.25	127.49	-	-	-
C-4'	-	-	-	141.42	31.74	-	-	-
CH_2	-	-	-	-	-	-	-	50.00

*C=N

Table 4: IR and mass spectra data of compounds (II-XIV)

Compounds	IR (cm^{-1})	MS *m/z* (%)
II	3477, 361, 1666	175 [M^+] (93), 176 [M^+ +1] (11.53)
III	1692,1707	318 [M^+] (22.09), 319 [M^+ +1] (4.76),
IV	1684,1612, 3472, 3372.29, 3410	297 [M^+ +3] (0.12), 292 [M^+ –2] (0.12)
V	1697, 3406, 3382	250 [M^+ –1] (0.54), 235[M^+ –NH_2] (3.15)
VI	1706, 3467 (br), 1595, 2919, 2850	327 [M^+ –C_8H_{14}] (1.29) 326 [M^+ –C_8H_{15}] (1.29)
VII	1669, 1593, 3460, 3296	176[M^+ –NH_3] (17.52), 161 [M^+ –SH+H] (27.03)
VII	1676, 2562, 2515, 23435, 3272	386[M^+] (7.35) 387[M^+ +H] (3.63)
IX	1677, 1722, 2560, 2850, 2922, 3554, 3476, 3412, 1264.	353 [M^+ +4] (10.75), 352 [M^+ +3] (2.69)
XI	1686 (br, st) 2969, 2898, 433439 (br, st)	343 [M^+] (76.73), 344 [M^+ +1] (100)
XII	1670, 1681, 2934, 2871, 3421 (br), 151	313 [M^+ – CH_2S] (2.42), 274 [M^+ –C_4H_7S+2H] (4.50)
XII	1670, 1588, 2969, 2927, 3324	390 [M^+ +1] (0.94), 392 [M^+ +3] (0.85)
XV	1677, 2968, 2875, 3265 (br)	292[M^+ –C_4H_{15}] (33.74), 274 [M^+ C_6H_{14}+5H] (3.14)

Table 5: ^{1}H and ^{13}C-NMR Spectra data of compounds (XV and XVIa)

Compound carbon no.	XV		XVIa	
	δ (ppm) ^{13}C	δ (ppm) of ^{1}H (*J*) Hz	δ (ppm) ^{13}C	δ (ppm) of ^{1}H (*J*) Hz
C-1	-	-	114.65	-
C-2	161.59	-	141.68	-
C-3	-	-	120.59	7.68 (1H, d, ^{3}J=8.07)
C-4	129.63	-	134.56	7.57 (1H, t, ^{3}J=7.52)
C-5	167.87	-	122.49	7.86 (1H, t, ^{3}J=7.71)
C-6	-	-	124.72	8.20 (1H, d, ^{3}J=8.07)
ph-CO	-	-	168.63	-
OCH_3	-	-	52.16	3.77 (3H, s)
C-2'	125.94	-	164.02	-
C-4'	-	-	164.02	-
C-5'	-	-	133.72	-
C-1''	-	-	129.36	-
C-2'' and C-6''	129.93	8.04 (2H, d, ^{3}J=6.97)	127.68	7.24 (4H, m) H-C-2'', H-C-3'', H-C-5'', H-C-6'')
C-3'' and C-5''	128.06	7.69-7.59 (3H, m)	128.29	7.24 (4H, m) H-C-2'', H-C-3'', H-C-5'', H-C-6'')
C-4''	125.94		130.57	7.34 (1H, t, ^{3}J=6.24)
H-olefinic	-	8.44 (1H, s)	132.09	7.43 (1H, s)
C-1'''	-	-	115.34	-
C-2'''	-	-	151.85	-
C-3'''	-	6.74 (1H, s)	98.04	6.22 (1H, s)
C-4'''	-	-	150.55	-
C-5'''	-	-	143.39	-
C-6'''	-	7.50 (1H, s)	112.68	6.57 (1H, s)
(OCH_3)-C-2'''	57.17	3.92 (3H, s)	57.49	3.63 (3H, s)
(OCH_3)-C-4'''	56.55	3.90 (3H, s)	56.11	3.61 (3H, s)
(OCH_3)-C-5'''	3.84 (3H, s)	3.84 (3H, s)	56.11	3.55 (3H, s)

Table 6: IR and mass spectra data of compound (XV-XVIa,b)

Compounds	IR (cm^{-1})	MS *m/z* (%)
XV	1791, 2995, 2941, 2834, 3061	339 [M^+] (42.35), 340 [M^+ +1] (9.11)
XVIa	1678, 1702	473 [M^+ +1] (3.86), 472 [M^+] (10.16)
XVIb	1607, (br), 1684	552 ($C_{27}H_{23}{}^{81}Br N_2 O_6$) (5.69), 550 [$M^+$] ($C_{27}H_{23}{}^{79}Br N_2 O_6$) (2.68)

Table 7: ^{1}H NMR spectra data of compounds (XIX and XX)

Compounds carbon. no	XIX		XX
	δ (ppm) ^{13}C	δ (ppm) ^{1}H (*J*) Hz	δ (ppm) ^{1}H (*J*) Hz
C-2	168.20	-	-
C-4	172.64	-	-
C-4a	141.34	-	-
C-5	-	-	8.22 (1H, s)
C-6	130.45	9.31 (2H, s)	8.34 (1H, s)
C-7	131.71	9.31 (2H, s)	-
C-8a	170.64	-	-
C-1'	125.07	8.38 (2H, dd)	-
C-2' and C-6'	121.63	8.34 (2H, dd)	-
C-3' and C-5'	118.54	-	-
C-4'	141.34	-	-
NH_2	-	10.79 (2H, s)	-
(CH_3)-C-2	25.74	2.12 (3H, s)	2.25 (3H , s)
OH	-	-	9.52 (1H , s)
NH	-	-	7.83 (1H , br, s)

Method 2

A mixture of the appropriate 2-phenyl-4-(2,4,5-trimet hoxy-benzylidene)-4*H*-oxa zol-5-one (XV) (0.01 mol) and methyl anthranilate (0.01 mol) in glacial acetic acid (5 ml) containing freshly fused sodium acetate (0.003 mol) was heated in water bath with continuous stirring for 3 h. The product was isolated after separation by column chromatography using sephadex LH-20. The physical and spectral data are shown in Tables 1, 5 and 6.

Methyl 5-bromo-2-[5-oxo-2-phenyl-4-(2,4,5- trimetho xybenzylidene)-4,5-dihydro-imidazol-1-yl] benzoic acid. (XVIb)

Method 1

A mixture of (XV) (0.01 mol) and methyl 5-bromo-anthranilate (0.01 mol) was fused in dry condition for 6 h. The product was then washed with ethanol and crystallized from dioxane. The physical and spectral data are shown in Tables 1 and 6.

Method 2

A mixture of (XV) (0.01 mol) and methyl 5-bromoanthranilate (0.01 mol) in glacial acetic acid (5 ml) containing freshly prepared fused sodium acetate (0.003 mol) was heated in boiling water bath with continuous stirring for 8 h then washed with ethanol. Physical and spectral data are shown in Tables 1 and 6.

2-Methyl-pyrazino [2,3-d][1,3]oxazin- 4-one (XVIII)

A mixture of acetic anhydride (50 ml) and

3-aminopyrazino-2-carboxylic acid (0.03 mol) was refluxed for 25 min. The solvent was then removed and the obtained solid was filtered, washed and crystallized from acetic acid. The physical is shown Table 1.

3-(4-Aminophenyl) -2-methyl- 3H-pteridinone (XIX)

2-Methyl-pyrazin o[2,3-*d*][1,3]ox azin-4-one (XVIII) (0.1 mol) and *p*-phenyle nediamine (0.1 mol) were heated under reflux in dry pyridine for 8 h. The reaction was cooled and treated with cold 10% hydrochloric acid. The separated solid was washed with water and crystallized from ethanol. The physical and spectral data are shown in Tables 1, 7 and 8.

5,5-Dimethyl-2-((4-(2-methyl-4-oxopteridin-3 (4H)-yl) phenylamino) methyl)-cyclohexane-1,3-dione (XXI)

A mixture of 5,5-dimethyl-1,3-cyclohexanedione (0.01 mol), compound 3-(4-amino-phenyl)-2-methyl-3*H*-pteridin-4-one (XIX) and formaldehyde (0.02 mol) in MeOH (60 ml) was warmed for 30 h. The solvent was then removed under reduced pressure. The product was filtered off, washed with *n*-hexane purified by column chromatography. The spectral data are shown in Tables 1, 7 and 8.

Pharmacology

Animals

Swiss albino mice (27-30 g birth Weight (bw)) of either sex were used throughout this study. Animals were maintained under standard conditions of temperature (23 ± 1.0°C), humidity (55 ± 10%), and light (approximately 12/12 h light/dark cycle) and fed on standard pellet diet with water *ad libitum*. Unnecessary disturbance of animals is avoided. The dose of each chemical compound was calculated accurately. Animals were allowed to adapt to the laboratory environment for 1 week before experimentation. All procedures were carried out in accordance with the Institutional Ethical Committee approval.

Preparation of the tested chemical compounds

All the tested chemicals and the reference drug (diazepam) were dissolved in 2% v/v DMSO before oral administration to the experimental animals.

Acute toxicity experiment

Mice in groups of six were given the tested compounds orally in graded doses (50-4000 mg/kg bw). Control animals received the vehicle (2% v/v DMSO) and kept under the same conditions without any treatment. Toxic symptoms and number of mice, which died in each group, were recorded after 48 h observation.

Doses

In this investigation, an experimental dose of 100 mg/kg that equal to one-tenth LD_{50} of most of the test compounds were selected to be given orally to mice. The reference drug, diazepam, was given orally at a certain dose (7.5 mg/kg). This dose was calculated by converting the therapeutic dose that used in human to mouse's dose according to the table of Paget and Barnes (1964).

Anticonvulsant activity

All the test compounds were screened for their anticonvulsant activity in Swiss albino mice by using two seizure models; Strychnine-induced convulsion test and the maximal electroshock seizure (MES) test.

Table 8: IR and mass spectra data of compound (XIX-XXI)

Compound	IR (cm^{-1})	MS *m/z* (%)
XIX	1677, 3468, 3413	256 [M^+ +3] (0.12), 241[M^+ –CH_3+3H] (0.12)
XX	1699, 1718, 3447	137 [M^+ –COOH+H] (32.16), 122 [M^+ –$C_2H_4O_2$+H] (0.64)
XXI	1670, 1728, 2950, 2925	392[M^+ –CH_3+2H] (0.44), 386[M^+ –CH_7] (0.42)

Table 9: Effect of the target compounds on strychnine-induced convulsions in mice

Treatments	Dose (mg/kg)	Latency to the seizure onset (min)
Normal control	00	0.00±0.00
Strychnine control	2.5	4.60±0.25
Diazepam	7.5	19.63±0.90*
1 Ref	100	13.86±1.28*
II	100	5.70±0.23
III	100	8.48±0.31*
IV	100	6.11±0.26
IV	100	11.01±0.69*
XII	100	15.01±0.98*
XIII	100	11.75±0.79*
XIV	100	5.88±0.30

Values represent the mean±S.E. of six mice for each group. *P<0.05: Statistically significant from strychnine control (dunnett's test)

Table 10: Anticonvulsant activity of target compounds in mice using maximal electroshock model

Treatments	Dose (mg/kg)	Mean threshold electrical current that induced seizure (mA)
Control	00	3.0±0.29
Diazepam	7.5	8.3±0.70*
I Ref	100	7.5±0.48*
II	100	2.3±0.17
III	100	4.5±0.34*
IV	100	3.8±0.31
IV	100	5.5±0.48*
XII	100	5.8±0.36*
XIII	100	5.8±0.31*
XIV	100	3.3±0.17

Values represent the mean ± S.E. of six mice for each group. *P<0.05: Statistically significant from control (dunnett's test)

Strychnine-induced convulsion test

Strychnine-induced convulsion test was carried out as described by Kaputlua and Uzbay (2009). Sixty-six mice were divided into 11 groups of 6 animals each. Mice of the first (normal control) and second (strychnine control) groups were treated orally with the vehicle in a dose of 5 mL/kg. Mice of the third group (reference) were treated orally with the diazepam in a dose of 7.5 mg/kg. Animals of the 4^{th} to 11^{th} groups were orally given the test compounds in a dose equal to one-tenth their LD_{50} (100 mg/kg). One hour post-medication, mice of groups 2-11 were injected IP with strychnine nitrate in a dose of 2.5 mg/kg and observed for

the onset of tonic hind-limb extension. The ability of the test compounds to prevent this feature or delay the onset of hind-limb extension was considered as an indication of anticonvulsant activity.

Maximum electroshock seizure test

MES test was performed in mice as described by Loscher *et al*. (1984). Sixty mice were divided into 10 groups and medicated orally with diazepam and the test compounds as those in strychnine-induced convulsion test (except the 2nd group). One hour after medication, mice were subjected to different levels of an alternating electrical current by Ugo Basile convulsiometer (Pulse generator 57800-001), through ear clip electrodes for 0.2 s. The mean threshold electrical current that induced tonic hind-limb extensor seizure was determined in each group.

Statistical analysis

Data were expressed as mean ± SEM with *n* indicating the number of replicates for a given experiment. Data were analyzed by one-way analysis of variance (ANOVA) followed by Dunnett's *post-hoc* test for multiple comparisons. Results were considered significant at $P < 0.05$.

Results and Discussion

Chemistry

The synthetic strategy to obtain the target compounds (I-XXI) is illustrated in schemes (I-V). 2-Methyl-1, 3-benzaoxazin-4-one (I), was obtained through reaction of anthranilic acid with acetic anhydride by heating under reflux or applying microwave irradiation, which was further reacted with $NH_2NH_2.H_2O$ to produce compound (II). Compounds (III) and (IV) were isolated after purification by column chromatography.

Compound (V) was obtained by three methods; the first two methods were by condensation of compound (I) with *p*-phenylinediamine in presence of glacial acetic acid or dry pyridine. The third method was by microwave irradiation of anthranilic acid, *p*-phenylinediamine, acetic anhydride mixture.

Compound (VI) was synthesized using compound (V) with formaldehyde and 3-methyl-phenyl-pyrazol-5-one (Scheme 1).

Compound (VII) was prepared from the reaction of methyl anthranilate with CS_2 and $NH_2NH_2.H_2O$. Compound (VIII) was obtained during the purification of compound (VII) using. Also compound (IX) was synthesized by reaction of (VII) with thiobarbituric acid and formaldehyde (Scheme 2). Compounds (XI–XIV) were prepared by reacting 3-amino-2-isopropyl-4 (3*H*) quinazolinone (X) with barbituric acid, thiobarbituric acid, 3-methyl-phenyl-pyrazol-5-one and/or 4,4-dimethyl-1,3-cyclohexanedione under Mannich reaction condition to yield compounds (XI-XIV), respectively (Scheme 3).

Upon treatment of benzoylglycine with 2,4,5-trimethoxybenzaldehyde; compound (XV) was produced, which was further reacted with methyl anthranilate or 5-bromo analogue to produce compounds (XVIa, b) by fusion. Some unsuccessful trails were carried out to prepare compounds (XVIIa, b) *via* the reaction between compounds (XVIa, b) and $NH_2NH_2.H_2O$ (Scheme 4).

2-Methyl-pyrazino [2,3-*d*][1,3]oxazin-4-one (XVIII) was obtained by refluxing of 3-amino-pyrazine-2-carboxylic acid and acetic anhydride. The latter compound was further reacted with *p*-phenylinediamine in presence of glacial acetic acid.

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During purification of compound (XIX), compound (XX) was obtained. Unsuccessful attempts were carried out for preparation of compound (XIX) by reacting compound (XVIII) with *p*-phenylenediamine under microwave irradiation; in contrast. this compound was obtained successfully from the reaction of 3-amino-pyrazine-2-carboxylic acid, acetic anhydride and *p*-phenylinediamine under microwave irradiation. Furthermore, compound (XIX) was allowed to react with 5,5-dimethyl-1,3-cyclohexanedione (Dimedone) and formaldehyde to produce (XXI) (Scheme 5).

Pharmacology

Acute toxicity (LD50) test

The tested compounds are characterized by a low degree of toxicity. Oral administration of the new compounds in doses up to 200 mg/kg failed to kill any mouse within 48 h of observation. The calculated LD_{50} of the tested chemicals in mice was found to be above 960 mg/kg. LD_{50} of compounds 1 Ref, XII and XIII was 970 mg/kg. LD_{50} of compounds II and III was 980 mg/kg. LD_{50} of compounds VI, IX and XIV was 1000 mg/kg. Accordingly, the new synthesized compounds are considered safe since substances possessing LD_{50} higher than 50 mg/kg are non-toxic (Buck *et al*., 1976).

Anticonvulsant activity

No alteration in the latency to the onset of seizure induced by strychnine (2.5 mg/kg, i.p.) in the animals pre-treated with compounds II, VI and XIV in a dose of 100 mg/kg was observed [Table 1]. Conversely, oral treatment of mice with compounds I Ref, III, IX, XII or XIII (100 mg/kg), 1 h before strychnine administration, alter the latency to the seizure onset when compared with the strychnine-treated group. They increased the latency (3.01, 1.84, 2.39, 3.26 and 2.55 times, respectively) to the onset of seizure induced by strychnine. In the electroshock investigation, the same compounds (I Ref, III, IX, XII and XIII) were found to be significantly active in mice [Tables 9 and 10]. They elevated the mean threshold electrical current required to induce tonic hind limb extensor seizure (7.5, 4.5, 5.5, 5.8 and 5.8 mA) in comparison to the control mice (3.0 mA).

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