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Synthesis and configurational assignment of 1,2-dihydroimidazo[5,1-*b*]quinazoline-3,9-diones: novel NMDA receptor antagonists

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ABSTRACT

NMDA receptors form a major subdivision of the ionotropic glutamate receptor family that mediates excitatory synaptic transmission in the brain. Series of 1-substituted 1,2-dihydroimidazo[5,1-*b*]quinazolinediones were synthesized and found to have potent nanomolar activity at the glycine site of the NMDA receptor. Imidazoquinazolinediones were prepared by cyclocondensation of 4-oxo-quinazoline-2-carboxamide with aldehydes and orthoesters with good yields. The formed enantiomers were separated by chiral HPLC. The absolute configuration of pure enantiomers is elucidated by combined CD/Quantumchemical time-dependent DFT calculation method (TDDFT).

1. Introduction

The excitatory amino acid neurotransmitter system is the key component for rapid synaptic excitation in the central nervous system of mammals.[1] The glutamate transmitter system has captured worldwide attention because it not only mediates standard fast excitatory synaptic transmission, but also participates in more complex neuronal processes, such as development, learning and memory, and even neuropathology.[2,3] Glutamate receptors have been implicated in various neurological diseases and conditions, including epilepsy, stroke, Alzheimer's disease, Parkinson's disease, Huntington's disease.[4] Selective modulation of glutamate receptor subtypes is expected to have enormous therapeutic potential in treatment of neurodegenerative disorders.[5,6]

The release of glutamate stimulates postsynaptic receptors for excitatory amino acids, which are divided into two large groups—metabotropic and ionotropic receptors.[7] Ionotropic receptors include *N*-methyl-D-aspartic acid (NMDA), 2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid (AMPA), and kainic acid receptors, which in turn include several subtypes.[8,9] NMDA receptors are glutamate-gated ion channels with high calcium permeability. Glutamate is the principal neurotransmitter; glycine has most likely a modulatory, albeit critical, role. Competitive antagonists at the glutamate site profoundly disturb synaptic transmission and are incompatible with most therapeutic interventions. Conversely, glycine-site agonists and antagonists have been used with promising results in a variety of disorders.[10,11]

There is much interest in ligand molecules acting on various subtypes of excitatory amino acid receptors and having the properties of partial agonists; the search for new ligands of NMDA receptors is therefore of current importance.

Various heterocyclic-fused chemical entities, including quinoxalines, quinolones, and quinazoline derivatives have been shown to harbor effective NMDA or AMPA antagonist effect in the glutaminergic system.[12,13] Quinazoline is among 'privileged' structures; a wide variety of pharmacological effects can be achieved by synthetic modifications on this bicyclic system.[14,15] Structural variants of heterocondensed quinazolines can afford new compounds for evaluation against a variety of biological targets.[16] Numerous biological applications have been attributed to imidazoquinazolines; and the group includes narcotic antagonists,[17] antihypertensives,[18] blood platelet aggregation inhibitors,[19,20] central nervous system stimulants,[21] tranquilizers,[22] anti-tumor agents,[23] PDE-5 inhibitors,[24] and anticonvulsants (Fig. 1).[25]

In spite of the interesting pharmacological properties of imidazo[1,5-*a*]quinazolines, very few synthetic and pharmacological reports have appeared in the literature on imidazo[5,1-*b*]quinazoline derivatives until recently.[26,27]

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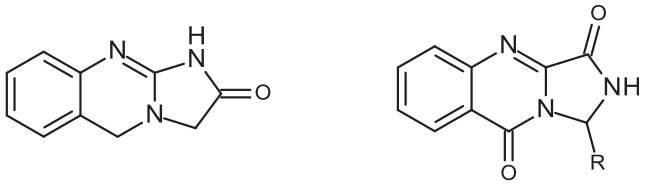


Fig 1. Linearly condensed imidazoquinazolinediones.

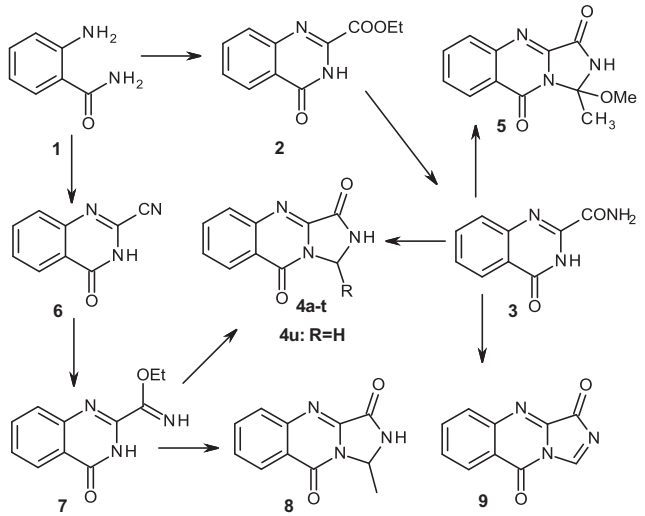
In addition, the 'kynurenine pathway', a cascade of enzymatic steps generates several biologically active endogenous compounds, including kynurenic acid,[28] which in micromolar concentrations may selectively antagonize NMDA receptors.[29,30] Such compounds, like imidazoquinazolones bearing modified functionality of kynurenic acid have potential NMDA antagonist properties. The angularly condensed imidazo[1,5-*a*]quinazolines have been reported to show a promising anticonvulsant profile.[31,25]

Recently, we developed quinazoline–alkyl-carboxylic acid derivatives as a new class of antagonists, which modulate excitatory synaptic transmission at the NMDA/AMPA receptor thus exhibiting strong anticonvulsant and antiepileptic activities.[32] In this paper we report the synthesis, stereochemistry, chiral properties, and glycine/NMDA affinities of imidazo[5,1-*b*]-quinazoline-3,9-diones as ring constrained tricyclic analogues of quinazoline–carboxylic acid derivatives.

2. Results and discussion

For the synthesis of imidazo[5,1-*b*]quinazolines two synthetic approaches are known: (a) condensation of anthranilic acid derivatives with substituted imidazolones[27] and (b) ring closure of 2-amino-alkyl-quinazolones.[26] 1-Dimethylamino-1,2-dihydro imidazo[5,1-*b*]quinazoline-3,9-dione was described as an intermediate for synthesis of aryl-substituted quinazolone-2-carboxamides prepared by cyclization of quinazolone-2-carboxamide with modified Vilsmeier formylation using DMF/*p*-toluenesulfonylchloride reagents at rt for 15 h. No structural characterization for the compound was given.[33] Earlier, we elaborated a synthetic method for linearly condensed imidazo[5,1-*b*]quinazolines by condensation of 2-aminoethylquinazolones with aliphatic and aromatic aldehydes.[34] Modification of this procedure was found suitable for the preparation of imidazo[5,1-*b*]quinazolindiones.

The synthetic routes to the prepared imidazoquinazolinediones are outlined in Scheme 1.



Scheme 1. Synthesis of imidazoquinazolinediones.

Starting from anthranilamide **1** the condensation reaction was performed with diethyl oxalate at 180 °C for 5 h.[35] The amidation of the ethyl 4-oxo-3*H*-quinazoline-2-carboxylate **2** led to the 2-carboxamide derivative **3**, which was cyclized with different aromatic and heteroaromatic aldehydes to imidazoquinazoline-3,9-diones **4a**–**t** in high yields. In the case of substituted-phenyl derivatives the cyclization was performed at 170 °C for 3 h. The ring closure reactions with aldehydes having lower boiling points were carried out at 130 °C for 10 h in the presence of small amounts of DMF. The yields, melting points, and HRMS data of the synthesized 1,2-saturated tricyclic compounds (**4a**–**t**) are found in Table 1.

The ^{1}H and ^{13}C NMR spectra of synthesized derivatives were completely assigned based on one, and homo- and heteronuclear two dimensional NMR experiments (COSY, HSQC, and HMBC). For numbering and detailed ^{1}H and ^{13}C NMR assignments, UV and IR absorption data of **4a**–**t** see Fig. 2 and Tables 2–4.

The reaction of quinazoline-2-carboxamide **3** with formaldehyde was carried out under pressure in sealed tube at 80 °C for 5 h to yield imidazo[5,1-*b*]quinazoline-3,9(1*H*,2*H*)-dione **4u**. Under the same conditions the other aliphatic aldehydes gave intermediates, which failed to cyclize. The use of acid or base catalysis did not facilitate the cyclocondensation. The reaction of **3** with trimethyl orthoacetate in the presence of sodium methoxide in methanol led to the formation of 1-methyl-1-methoxy-imidazo[5,1-*b*]quinazoline-3,9(1*H*,2*H*)dione **5**. Selective dehydration of **3** with excess phosphorus pentoxide in xylene at 130 °C for 3 h led to the 2-cyano derivative[36] **6**, which was treated with methanolic hydrochloric acid solution at ambient temperature to afford the 2-iminoether derivative **7**. Imino group in compound **7** is a better nucleophile, and therefore higher reactivity is expected in condensation reactions than that for **3**. The 2-iminoether was easily cyclized to compound **8** with acetaldehyde if the mixture was allowed to stand in ethanol at ambient temperature for 12 h.

The cyclization of 2-iminoether (**7**) derivative with benzaldehyde could be accomplished under milder reaction conditions by heating the reaction mixture at 100 °C for 3 h. After completion of the reaction the product imidazoquinazolinedione **4k** was separated after the fast hydrolysis of the iminoether derivative upon diluting the reaction mixture with water. Prolonged heating of quinazoline-2-carboxamide **3** with trimethyl orthoformate provided **9**.

2.1. Determination of the absolute configuration of 1-aryl-imidazo[5,1-*b*]quinazoline-1,9(1*H*,2*H*)-diones

The cyclization of quinazolin-2-carboxamide **3** with aromatic aldehydes generates a new stereogenic center at C-1, and hence it affords racemic mixtures. Since the stereochemistry of 1-aryl-imidazo[5,1-*b*]quinazoline-3,9(1*H*,2*H*)-diones have not been studied yet and there is no correlation reported between their stereochemistry and the characteristic ECD transitions, chiral HPLC–ECD analysis and TDDFT ECD calculation were carried out on a selected compound **4e**. Chiral HPLC separation of **4e** was achieved on β-cyclodextrin stationary phase using H_2O/MeOH 85:15 as eluent. Then online HPLC–ECD spectra of the baseline-separated enantiomers were recorded affording mirror image ECD curves. The first-eluting enantiomer has a broad positive Cotton effect (CE) at 306 nm with distinct vibrational fine-structure, a positive CE at 240 nm and a negative one at 223 nm (Fig. 3).

For the configurational assignment, the solution TDDFT ECD protocol has been pursued, which had been proved a powerful method for the stereochemical study of synthetic[37] and natural derivatives.[38,39] The MMFF conformational search of **4e** provided two initial conformers, the DFT reoptimization of which at the B3LYP/6-31G(d) level resulted in two slightly different conformers with 54 and 46% populations (Fig. 4).

Table 1
Physical and receptor binding data for compounds **4a**–**t**

Nr.	1-Substituent	Mp [°C]	Yield [%]	Formula	HRMS $[M+H]^+$ (calcd)	K_i [nM][a]
4a	4-$N(CH_3)_2$–C_6H_4	275–278	82	$C_{18}H_{16}N_4O_2$	321.1343 (321.1346)	250
4b	4-NHAc–C_6H_4	293–295	84	$C_{18}H_{14}N_4O_3$	335.1135 (335.1139)	8
4c	2-OH–C_6H_4	277–281	73	$C_{16}H_{11}N_3O_3$	294.0877 (294.0873)	19
4d	3-OH–C_6H_4	307–309	88	$C_{16}H_{11}N_3O_3$	294.0880 (294.0873)	58
4e	4-OH–C_6H_4	325–327	85	$C_{16}H_{11}N_3O_3$	294.0876 (294.0873)	21
4f	4-OH–3-OMe–C_6H_3	285–288	89	$C_{17}H_{13}N_3O_4$	324.0983 (324.0979)	79
4g	4-OMe–C_6H_4	274–277	57	$C_{17}H_{13}N_3O_3$	308.1024 (308.1030)	17
4h	3,4-$(OMe)_2$–C_6H_3	245–248	75	$C_{18}H_{15}N_3O_4$	338.1134 (338.1135)	54
4i	3,4,5-$(OMe)_3$–C_6H_2	264–268	91	$C_{19}H_{17}N_3O_5$	368.1237 (368.1241)	
4j	4-CH_3–C_6H_4	288–291	83	$C_{17}H_{13}N_3O_2$	292.1079 (292.1081)	32
4k	C_6H_5	329–331	94	$C_{16}H_{11}N_3O_2$	278.0919 (278.0924)	
4l	$CH_2C_6H_5$	291–295	41	$C_{16}H_{11}N_3O_3$	292.1077 (292.1081)	
4m	4-Cl–C_6H_4	304–305	97	$C_{16}H_{10}ClN_3O_2$	312.0533 (312.0534)	11
4n	4-CF_3–C_6H_4	306–308	96	$C_{17}H_{10}F_3N_3O_2$	346.0794 (346.0798)	
4o	4-COOMe–C_6H_4	245–248	93	$C_{18}H_{13}N_3O_4$	336.0982 (336.0979)	89
4p	3-NO_2–C_6H_4	230–233	77	$C_{16}H_{10}N_4O_4$	323.0778 (323.0775)	
4q	2-Furyl	270 (dec)	73	$C_{14}H_{10}N_4O_2$	268.0720 (268.0717)	15
4r	2-Pyridyl	285–287	59	$C_{15}H_{10}N_4O_2$	279.0879 (279.0877)	
4s	3-Pyridyl	302–305	87	$C_{15}H_{10}N_4O_2$	279.0878 (279.0877)	
4t	3-Indolyl	292 (dec)	70	$C_{18}H_{12}N_4O_2$	317.1039 (317.1034)	

[a] Selected compounds.

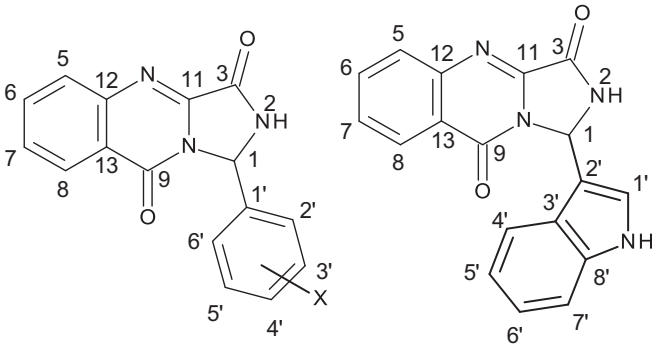


Fig 2. Numbering of 1-aryl-imidazo[5,1-*b*]quinazoline-3,9(1*H*,2*H*)diones (**4a**–**t**).

The two conformers differed only in the orientation of the hydroxyl hydrogen. TDDFT ECD calculations of both conformers were performed using various functionals (B3LYP, BH&HLYP, PBE0) and TZVP basis set, the Boltzmann-averaged spectra of which reproduced well the experimental ECD spectrum with BH&HLYP giving the best agreement. Since the BH&HLYP/TZVP Boltzmann-weighted spectrum of (*R*)-**4e** was near identical with the experimental HPLC–ECD curve of the second-eluted enantiomer (Fig. 3), the absolute configuration of the second-eluted enantiomer was determined as (*R*). This correlation between the chiroptical data and absolute configuration may serve as a reference to deduce the absolute configuration of analogous 1-aryl-imidazo[5,1-*b*]quinazoline-3,9(1*H*,2*H*)-diones with similar substitution pattern.

Table 2
^{1}H NMR data for compounds **4a**–**t**

Substituent	Nr.	1-Ar	H-5[a]	H-6[b]	H-7[c]	H-8[d]	Other protons	2-N*H*[e]	1-C*H*[f]
p-$N(CH_3)_2$	**4a**	7.23, d, 2H; 6.69, d, 2H	7.89	7.62	7.91	8.10	2.89, s, CH_3	10.49	6.53
p-NHAc–Ph	**4b**	7.59, d, 2H; 7.38, d, 2H	7.91	7.63	7.93	8.11	10.04, s, N*H*–Ac; 2.03, s, CH_3	10.56	6.57
o-OH	**4c**	7.35, d, 1H; 7.20, t, 1H; 6.84, t, 1H; 6.73, d, 1H	7.89	7.63	7.92	8.12	9.78, s, O*H*	10.35	6.64
m-OH	**4d**	7.20, t, 1H; 6.86, d, 1H; 6.78, d, 1H 6.76, s, 1H	7.92	7.64	7.94	8.13	9.57, s, O*H*	10.62	6.55
p-OH	**4e**	7.26, d, 2H; 6.77, d, 2H	7.89	7.62	7.92	8.10	9.69, s, O*H*	10.52	6.54
m-OMe-*p*-OH	**4f**	7.02, s, 1H; 6.85, d, 1H; 6.77, d, 1H;	7.89	7.62	7.92	8.11	9.25, s, O*H*; 3.73, s, CH_3	10.51	6.53
p-OMe	**4g**	7.39, d, 2H; 6.94, d, 2H	7.91	7.63	7.93	8.11	3.75, s, CH_3	10.56	6.59
3,4-$(OMe)_2$	**4h**	7.06, d, 1H; 7.00, dd, 1H; 6.95, d, 1H;	7.89	7.62	7.92	8.11	3.75, s, CH_3; 3.65, s, CH_3	10.53	6.57
3,4,5-$(OMe)_3$	**4i**	6.82, s, 2H	7.89	7.63	7.92	8.12	3.74, s, $CH_3\times2$; 3.65, s, CH_3	10.52	6.55
p-Me	**4j**	7.33, d, 2H; 7.21, d, 2H	7.90	7.63	7.92	8.10	2.30, s, CH_3	10.59	6.59
Ph	**4k**	7.48, m, 2H; 7.40, m, 3H	7.92	7.63	7.93	8.11		10.64	6.64
Benzyl	**4l**	7.12, m, 3H; 6.96, m, 2H	7.76	7.68	7.91	8.32	3.68, dd, CH_2(a); 3.24, dd, CH_2(b)	10.35	6.06
p-Cl–Ph	**4**	7.53, d, 2H; 7.46, d, 2H	7.91	7.64	7.93	8.11		10.62	6.65
p-CF_3	**4n**	7.78, d, 2H; 7.75, d, 2H	7.93	7.64	7.95	8.11		10.68	6.74
p-COOMe	**4o**	7.98, d, 2H; 7.65, d, 2H	7.92	7.66	7.94	8.11	3.86,s, CH_3	10.69	6.71
m-NO_2	**4p**	8.49, s, 1H; 8.27, d, 1H; 8.00, d, 1H; 7.70, t, 1H	7.91	7.64	7.94	8.11		10.69	6.85
Fur-2-yl	**4q**	7.67, d, 1H; 6.85, d, 1H; 6.51, m, 1H;	7.91	7.65	7.95	8.16		10.65	6.78
Pyridine-2-yl	**4r**	8.51, dd, 1H; 7.94, m, 1H; 7.78, d, 1H; 7.42, dd, 1H	7.92	7.64	7.95	8.12		10.63	6.75
Pyridine-3-yl	**4s**	8.82, d, 1H; 8.61, dd, 1H; 7.89, m, 1H; 7.42, dd, 1H	7.92	7.64	7.95	8.12		10.63	6.71
Indol-3-yl	**4t**	7.77, d, 1H; 7.41, d, 1H; 7.07, t, 1H; 7.02, d, 1H; 6.91, t, 1H	7.92	7.61	7.92	8.07	11.36, s, N*H*	10.56	6.94

[a] d, $J_{5-6}\approx7.8$ Hz, 1H.
[b] dd, $J_{6-7}\approx7.0$ Hz, 1H.
[c] d, $J_{7-8}\approx8.0$ Hz, 1H.
[d] d, 1H.
[e] s, 1H.
[f] s, 1H except for **4l**; t, J=3.2 Hz, 1H.

Table 3
^{13}C NMR data for compounds **4a**–**t**

Nr.	1	3	5	6	7	8	9	10	12	13	1′	2′	3′	4′	5′	6′	Other carbons
4a	69.1	159.2	128.4	128.1	134.8	125.9	157.8	121.8	121.8	148.5	121.4	128.2	111.9	151.1	111.9	128.2	40.0, $N(CH_3)_2$
4b	68.8	159.2	128.5	128.1	134.9	125.9	157.8	121.8	121.8	148.5	140.3	127.9	118.9	127.9	118.9	129.2	168.4, $C(O)CH_3$; 24.0, $C(O)CH_3$
4c	67.6	160.0	128.4	127.9	134.8	125.9	157.7	121.6	121.6	148.6	120.1	155.6	116.0	130.5	119.0	130.3	
4d	68.8	159.2	128.5	128.2	135.0	126.0	157.6	121.7	121.7	148.4	136.5	113.6	157.7	116.4	129.8	117.7	
4e	68.9	159.2	128.5	128.1	134.9	125.9	157.8	121.8	121.8	148.5	125.0	128.8	115.3	158.8	115.3	128.8	
4f	69.2	159.2	128.4	128.1	134.8	125.9	157.9	121.9	121.9	148.5	125.5	111.4	147.7	147.6	115.3	120.3	55.8, OCH_3
4g	68.7	159.2	128.5	128.1	134.9	125.9	157.8	121.8	121.8	148.5	126.6	128.8	114.0	160.1	114.0	128.8	55.2, OCH_3
4h	69.1	159.2	128.4	128.1	134.8	125.9	157.9	121.8	121.8	148.5	127.1	110.8	148.7	149.7	111.6	120.2	55.7, 3′-OCH_3; 55.6, 4′-OCH_3
4i	69.4	159.3	128.4	128.0	134.8	126.0	158.1	121.8	121.8	148.5	130.6	104.9	153.0	138.2	153.0	104.9	60.0, 4′-OCH_3; 56.1, 3′,5′-$OCH_3\times2$
4j	68.9	159.2	128.5	128.1	134.9	125.9	157.7	121.7	121.7	148.5	132.1	127.3	129.2	139.0	129.2	127.3	20.8, CH_3
4k	69.0	159.3	128.5	128.2	134.9	125.9	157.8	121.7	121.7	148.5	135.2	127.4	128.7	128.7	128.7	127.4	
4l	67.2	159.2	128.4	128.2	135.0	126.1	158.7	121.2	121.2	148.1	132.4	130.0	128.1	128.1	128.1	130.0	35.7, CH_2
4m	68.3	159.3	128.5	128.2	135.0	125.9	157.9	121.7	121.7	148.5	134.2	129.5	128.7	129.5	128.7	134.1	
4n	68.3	159.4	128.6	128.3	135.1	126.0	157.9	121.7	121.7	148.5	139.8	128.5	125.6[a]	129.9	125.6[b]	128.5	123.9,[c] CF_3
4o	68.4	159.3	128.6	127.9	135.0	126.0	157.9	121.7	121.7	148.5	140.2	127.9	129.5	130.6	129.5	127.9	165.7, $COOCH_3$; 52.3, $COOCH_3$
4p	67.9	159.5	128.5	128.2	134.9	125.9	158.0	121.7	121.7	148.5	137.4	123.0	147.8	124.4	130.3	134.1	
4q	62.3	159.3	128.0	127.8	134.2	125.3	157.2	121.5	121.5	148.5	136.9	110.7	110.5	143.3			
4r	68.9	159.8	128.6	128.2	135.1	125.9	157.6	121.6	121.6	148.6	153.4		150.0	124.6	137.4	123.9	
4s	67.1	159.4	128.5	128.2	134.9	125.9	158.0	121.7	121.7	148.5	130.9	149.5		150.6	135.0	123.8	
4t	64.8	159.3	128.5	128.1	134.8	125.9	157.8	121.8	121.8	148.4	124.1	107.4	127.3	119.5	121.5	121.5	136.5 (8′), 112.2 (7′)

[a] q, $J_{13C\text{-}19F}$=3.6 Hz.
[b] q, $J_{13C-19F}$=31.8 Hz.
[c] q, $J_{13C\text{-}19F}$=272.4 Hz.

Table 4
UV and IR absorption data for compounds **4a**–**t**

Nr.	UV absorption	IR absorption			
	λ_{max} [nm], (log ε)	2NH	3C=O	9C=O	Other
4a	322 (3.75), 304 (3.96), 296 (4.06), 288 (3.99), 231 (4.55)	3224	1715	1676	
4b	321 (3.73), 303 (3.95), 294 (4.02), 285 (3.97), 231 (4.48)	3187	1718	1678	1645 $COCH_3$
4c	319 (3.71), 302 (3.93), 293 (3.97), 286 (3.96), 230 (4.44)	3215	1705	1679	3287 OH
4d	318 (3.76), 303 (3.95), 294 (3.98), 285 (3.95), 232 (4.43)	3281	1720	1680	3445 OH
4e	319 (3.72), 303 (3.94), 294 (3.99), 285 (3.98), 231 (4.46)	3246	1708	1681	3392 OH
4f	320 (3.72), 304 (3.94), 295 (4.01), 284 (3.97), 231(4.47)	3230	1697	1675	3435 OH
4g	318 (3.78), 293 (4.04), 286 (4.03), 230 (4.56)	3253	1706	1678	
4h	319 (3.77), 293 (4.01), 286 (3.99), 230 (4.59)	3278	1700	1681	
4i	319 (3.80), 293 (4.03), 286 (4.01), 230 (4.61)	3212	1703	1677	
4j	319 (3.82), 304 (4.04), 294 (4.08), 229 (4.49)	3219	1708	1678	
4k	319 (3.85), 303i (4.06), 294.5 (4.11), 229 (4.48)	3210	1720	1680	
4l	318 (3.81), 303 (4.07), 295 (4.05), 231 (4.39)	3243	1692	1673	
4m	319 (3.72), 303 (3.92), 294 (3.99), 285 (3.95), 234 (4.36)	3274	1723	1681	
4n	317 (3.76), 305 (3.94), 296 (4.04), 235 (4.51)	3321	1728	1688	
4o	321 (3.84), 306 (4.04), 297.5 (4.10), 239 (4.54)	3337	1721	1687	1743 COOMe
4p	320 (3.71), 303 (3.89), 295 (3.95), 234 (4.67)	3348	1722	1690	
4q	319 (3.74), 302i (4.03), 294 (4.11), 226 (4.36)	3213	1695	1672	
4r	316 (3.71), 301 (3.86), 292 (3.99), 228 (4.41)	3306	1716	1680	
4s	317 (3.85), 303 (4.06), 293 (4.05), 229 (4.53)	3312	1713	1684	
4t	319 (3.70), 303 (3.91), 294 (3.98), 287 (3.95), 233(4.36)	3246	1719	1670	

2.2. NMDA antagonist properties

Preliminary pharmacological testing of selected 1-aryl-imidazoquinazolinediones suggests that the compounds are highly potent antagonists with nanomolar affinity in the [3*H*]5,7-dichlorokynurenic acid binding assay[40] for NMDA receptors (Table 1).

The most active compounds of the series were the 4-substituted-aryl derivatives. The size of the functional group had no marked effect on the activity profile.

In conclusion, we synthesized 1-substituted derivatives of imidazoquinazolindione by thermal cyclocondensation of 4-oxo-quinazoline-2-carboxamide with a series of aldehydes. Absolute configuration of separated enantiomers was determined by comparison of the online HPLC–ECD spectra with the computed TDDFT ECD spectra. Such promising compounds may act as lead molecules for future investigations of novel NMDA receptor subsite selective drugs.

3. Experimental

3.1. General

All chemicals were purchased from Sigma–Aldrich Chemicals (Darmstadt, Germany) and were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VNMRS nuclear magnetic resonance spectrometer (600 MHz for ^{1}H, 150.9 MHz for ^{13}C) equipped with a dual 5-mm inverse-detection gradient (IDPFG) probehead. Spectra were recorded in DMSO-d_6 or $CDCl_3$ at 25.0±0.1 °C and referenced to internal standard Me_4Si. NMR spectra were processed with both VNMRJ 2.2C and MestReNova software (ver. 6.1.1.). The structure of the compounds was confirmed by 1D (^{1}H, ^{13}C) and 2D NMR (HSQC, HMBC, COSY) spectra. Melting points were taken on a Stuart SMP-3 apparatus. The high-resolution accurate masses (HRMS) were determined with an Agilent 6230 time-of-flight mass spectrometer. Samples were introduced by the

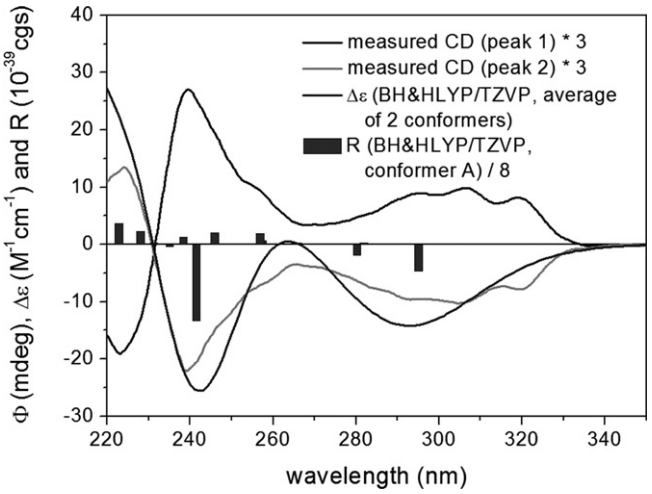


Fig 3. Online HPLC–ECD spectra of the first- (black) and second-eluting (gray) enantiomers of **4e** in H_2O/MeOH 85:15 compared with the Boltzmann-weighted BH&HLYP/TZVP spectrum (blue) calculated for the two lowest-energy conformers of the (*R*)-enantiomer. Bars indicate the calculated rotatory strengths of conformer A.

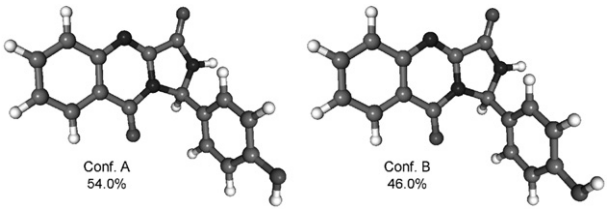


Fig 4. DFT optimized geometries and populations of the two low-energy conformers of (*R*)-**4e**.

Agilent 1260 Infinity LC system, the mass spectrometer was operated in conjunction with a Jet Stream electrospray ion source in positive ion mode. Reference masses of *m*/*z* 121.050873 and 922.009798 were used to calibrate the mass axis during analysis. Mass spectra were processed using Agilent MassHunter B.02.00 software. UV spectra were recorded on Jasco V-550 spectrometer with 1 cm cuvettes in ethanol solution at 25 °C. IR spectra were recorded from KBr discs on a. Perkin-Elmer 1600 FTIR instrument. ECD spectra were recorded on Jasco J-720 instrument. The liquid chromatograph consisted of a Jasco PU-980 Intelligent HPLC pump with a Rheodyne 7725i injector (Cotati, CA, USA), and a Jasco UV-975 Intelligent UV/VIS detector. For the chiroptical detection of the resolved enantiomers a cylindrical, focusable flow through cell was applied in to the spectropolarimeter sample compartment. The β-cyclodextrin column (250×4.6 mm; 5 mm) was purchased from ChiroQuest (Budapest, Hungary). The mobile phase contained 15 v/v% methanol and 85 v/v% purified water. The eluent components were degassed before mixing and have been sonicated for 10 min after mixing. The eluent flow was set to 0.8 mL/min. TLC was carried out on TLC aluminum sheets, Kieselgel 60 F_{254} (Merck KGaA, Darmstadt, Germany). In silico calculations were carried out on an Intel Core i7-950 PC by using MMFF force-field method in Macromodel, and B3LYP/6-31G(d), B3LYP/TZVP, BH&HLYP, and PBE0/TZVP methods in the Gaussian 03 program package.

3.2. Computational section

Mixed torsional/low mode conformational searches were carried out by means of the Macromodel 9.7.211[41] software using Merck Molecular Force Field (MMFF) with implicit solvent model for water. Geometry reoptimizations at B3LYP/6-31G(d) level of theory followed by TDDFT calculations using various functionals (B3LYP, BH&HLYP, PBE0) and TZVP basis set were performed by the Gaussian 03 package.[42] Boltzmann distributions were estimated from the ZPVE corrected B3LYP/6-31G(d) energies. ECD spectra were generated as the sum of Gaussians[43] with 3000 cm^{-1} half-height width (corresponding to ca. 17 nm at 240 nm), using dipole-velocity computed rotational strengths. The MOLEKEL[44] software package was used for visualization of the results.

3.3. Chemical synthesis

*3.3.1. Ethyl-4(3H)-oxo-quinazoline-2-carboxylate (**2**).* A mixture of anthranilamide **1** (50 g) and diethyl oxalate (110 mL) was refluxed in oil bath at 185–186 °C for 4.5 h. The reaction mixture exhibited a yellowish green fluorescence. Excess of diethyl oxalate was removed by distillation under reduced pressure. The brownish residue was triturated with cold ethanol, filtered, dried, and crystallized from ethanol to give 63 g (78%) of **2** as colorless crystals, mp 192–194 °C, lit. 189 °C.[35]

*3.3.2. 4(3H)-Oxo-quinazoline-2-carboxamide (**3**).* A suspension of 40 g (0.18 mol) of **2** in 25%. NH_4OH (200 mL) was heated at 70 °C for 2 h. The reaction mixture was allowed to stand at room temperature overnight. The pH of the mixture was set to neutral with acetic acid and the precipitated crystals were filtered and washed with water and cold ethanol to give 34 g (98%) of **3** as colorless powder, mp 231–233 °C, lit. 230 °C.[45]

*3.3.3. General procedure for preparation of 1-aryl-imidazo[5,1-b] quinazoline-3,9(1H,2H)diones (**4a**–**t**).* The well-homogenized equimolar mixture of **3** and the appropriate aromatic aldehyde was heated at 170 °C for 3 h. After completion of the reaction (TLC control, silica gel; benzene/methanol 4:1), the semisolid waxy residue was suspended in 3 mL ethanol, and sonicated for 1 h at 60 °C. The resulting precipitate was filtered and washed with ethanol. The crude products were recrystallized from DMF/ethyl acetate (Tables 1–4).

*3.3.3.1. 1-Phenyl-imidazo[5,1-b]quinazoline-3,9(1H,2H)dione (**4k**).* To a stirred suspension of **7** hydrochloride (0.5 g, 2 mmol) in dioxane (5 mL) was added benzaldehyde (0.2 mL, 2 mmol). The reaction mixture was then heated at 100 °C for 3 h. The solvent was evaporated, the residue diluted with 5% hydrochloric acid (5 mL), and stirred for 30 min. The precipitated product was filtered and washed with water. The crude product was crystallized from ethanol to give **4k** as colorless crystals (0.35 g, 64%) (Tables 1–4).

*3.3.3.2. Imidazo[5,1-b]quinazoline-3,9(1H,2H)-dione (**4u**).* A mixture of **3** (1.89 g, 0.01 mol), paraformaldehyde (0.36 g, 0.012 mol), and triethylamine (two drops) in dimethylformamide (3 mL) was stirred in a sealed tube at room temperature for 2 h, then heated for 8 h until the disappearance of amide (checked by TLC). The reaction mixture was diluted with water (20 mL). The separated solid was filtered and washed with water. The crude product was dissolved in chloroform (20 mL), the insoluble material was filtered, and the solution washed with 5% sodium carbonate solution (2×10 mL) and water (10 mL), then dried over sodium sulfate. The solvent was evaporated and the residue was crystallized from isopropanol to give **4u** as colorless crystals (1.14 g, 56%), mp: 251–252 °C (decomp.). Found: C 9.74; H 3.50; N 20.85. $C_{10}H_7N_3O_2$ requires: C 9.70; H 3.51; N 20.89%; UV (EtOH): λ_{max} (log ε)=315 (3.80), 301 (4.01), 295 (3.95), 231 (4.24) nm; IR (KBr): ν_{max}=3163 (NH), 1702 (C=O), 1673 (C=O) cm^{-1}; δ_H (600 MHz, $CDCl_3$) 8.11 (1H, dd, *J* 8.1, 1.1 Hz), 7.93 (1H, dd, *J* 8.1, 1.1 Hz), 7.87 (1H, ddd, *J* 8.0, 7.1, 1.2 Hz), 7.63 (1H, dt, *J* 7.8, 0.9 Hz), 5.86 (1H, d, *J* 13.1 Hz), 5.31 (1H, d, *J* 13.1 Hz); δ_C (150 MHz, $CDCl_3$)

161.6, 159.2, 150.7, 145.7, 134.3, 130.5, 128.2, 126.1, 124.2, 48.3; HRMS: $[M+H]^+$, found: 201.0538. $C_{10}H_7N_3O_2$ requires: 201.0548.

*3.3.4. 1-Methyl-1-methoxy-imidazo[5,1-b]quinazoline-3,9(1H,2H)dione (**5**).* Compound **3** (1.89 g, 0.01 mol) was suspended in a solution of sodium methoxide (8.3%) in methanol (20 mL) under efficient stirring at room temperature. Then a mixture of 10 mL methanol and 2.50 mL (0.02 mol) methyl orthoacetate was added drop-wise into this suspension for 1 h, and the mixture was stirred for another 1 h. Then the reaction mixture was refluxed for 10 h. HCl (36%) was used to adjust the pH to 4 and the temperature was kept below 30 °C. Then the mixture was filtrated and the solvent was evaporated to obtain a colorless powder, which was then refluxed in 10 mL methanol for 20 min. Insoluble residue was removed by filtration and the filtrate was kept in the refrigerator for 12 h to obtain 1.25 g (51%) of **5** as colorless crystals, mp 204–206 °C. Found: C 58.77; H 4.52; N 17.13. $C_{12}H_{11}N_3O_3$ requires C 58.77, H 4.52, N 17.13%; UV (EtOH): λ_{max} (log ε)=317 (3.80), 302 (4.06), 294 (4.01), 233 (4.39) nm; IR (KBr) ν_{max}=3260 (N–H), 1678 (C=O), 1615 (C=N) cm^{-1}; δ_H (600 MHz, $CDCl_3$) 8.23 (1H, dd, *J* 8.0, 1.2 Hz), 7.95 (1H, dd, *J* 8.0, 0.9 Hz), 7.87 (1H, ddd, *J* 8.0, 7.1, 1.2 Hz), 7.63(1H, dt, *J* 7.8, 0.9 Hz), 3.32 (3H, s), 1.71 (3H, s); δ_C (150 MHz, $CDCl_3$) 159.8, 158.5, 151.7, 148.2, 134.5, 131.4, 128.5, 126.2, 123.6, 88.7, 51.3, 18.5; HRMS: $[M+H]^+$, found: 245.0798. $C_{12}H_{11}N_3O_3$ requires: 245.0800.

*3.3.5. 4(3H)-Oxo-quinazoline-2-carbonitrile (**6**).* To a suspension of **3** (1.89 g, 0.01 mol) in toluene (10 mL) was added excess phosphorus pentoxide (4.23 g, 0.03 mol) and the mixture was stirred at 110 °C for 3 h. The solvent was evaporated in vacuo, the residue suspended in water (20 mL), and neutralized with sodium carbonate. The water layer was extracted with chloroform (3×10 mL). The combined organic phases were washed with water (2×10 mL) dried over sodium sulfate, decolorized by charcoal, and evaporated. The residue was crystallized from ethyl acetate/hexane to give **6**[36] 1.60 g (84%), mp>240 °C (decomp.). Found: C 63.19; H 2.92; N 24.58. $C_9H_5N_3O$ requires: C 63.16; H 2.94; N 24.55%; UV (EtOH): λ_{max} (log ε)=227 (4.14), 238 (4.20), 253 (4.05), 312 (3.81) nm; IR (KBr): ν_{max}=3317 (N–H), 2237 (CN), 1686 (C=O) cm^{-1}; δ_H (600 MHz, DMSO-d_6) 8.18 (1H, dd, *J* 7.96 Hz), 7.59 (1H, m), 7.52 (1H, m), 7.36 (1H, m); δ_C (150 MHz, DMSO-d_6) 171.2, 150.7, 143.6, 126.5, 126.0 (2×), 132.4, 123.8, 118.1; HRMS: $[M+H]^+$, found: 171.0430. $C_9H_5N_3O$ requires: 171.0433.

*3.3.6. Ethyl-4(3H)-oxo-quinazoline-2-iminocarboxilate (**7**).* To a stirred solution of **6** (1.71 g, 0.01 mol) in $CHCl_3$ (15 mL) was added ethanol (5.8 mL, 0.1 mol). The solution was cooled to 0 °C and HCl was bubbled through the solution for 1 h. The reaction mixture was then stirred at room temperature for 4 h. To complete the conversion, the solution was cooled down to 0 °C and HCl was bubbled through the solution for another 1 h. The reaction mixture was then stirred at room temperature overnight. The solvent was evaporated, the residue was triturated in diethyl ether, and the resulting solid was collected by filtration to give 1.73 g (94%) of **7** hydrochloride as a colorless powder. Found: C 52.11; H 4.75; N 16.59; Cl 13.94. $C_{11}H_{12}N_3ClO_2$ requires: C 52.08; H 4.77; N 16.52; Cl 13.95%; UV (EtOH): λ_{max} (log ε)=223 (4.25), 241 (4.37), 248 (4.15), 316 (3.93) nm; IR (KBr): ν_{max}=3185 (N–H), 1672 (C=O), 1625 (C=N) cm^{-1}; δ_H (600 MHz, $CDCl_3$) 12.80 (2H, br s), 12.00 (1H, br s), 8.19 (1H, dd, *J* 7.9, 1.2 Hz), 7.62 (1H, ddd, *J* 8.2, 7.0, 1.5 Hz), 7.53 (1H, dd, *J* 8.2, 0.8 Hz), 7.38 (1H, dt, *J* 7.7, 0.8 Hz), 4.48 (2H, q, *J* 7.1 Hz), 1.51 (3H, t, *J* 7.1 Hz); δ_C (150 MHz, $CDCl_3$) 172.6, 160.2, 150.7, 144.3, 132.5, 127.2, 126.1, 126.1, 124.2, 66.8, 14.8; HRMS: $[M+H]^+$, found: 253.6859. $C_{11}H_{12}N_3ClO_2$ requires: 253.6862.

*3.3.7. 1-Methyl-imidazo[5,1-b]quinazoline-3,9(1H,2H)dione (**8**).* To a stirred solution of **7** hydrochloride (0.5 g, 2 mmol) in ethanol (5 mL) was added excess acetaldehyde (0.22 mL, 4 mmol). The reaction mixture was then stirred at room temperature overnight. The solvent was evaporated, the residue diluted with 5% hydrochloric acid (5 mL), and stirred for 30 min. The mixture was neutralized with 10% sodium carbonate solution and extracted with chloroform (3×10 mL). The combined organic phase was washed with water, decolorized by charcoal, dried over sodium sulfate, and evaporated. The solid residue was crystallized from ethyl acetate to give **8** as colorless crystals (0.27 g, 63%), mp 233–234 °C. Found: C 61.44; H 4.19; N 19.45. $C_{11}H_9N_3O_2$ requires: C 61.39; H 4.22; N 19.52%; UV (EtOH): λ_{max} (log ε)=317 (3.85), 305 (4.06), 295 (4.11), 231 (4.43) nm; IR (KBr): ν_{max}=3225 (NH), 1705 (C=O), 1678 (C=O); δ_H (600 MHz, $CDCl_3$) 8.16 (1H, dd, *J* 8.15, 1.10 Hz), 7.95 (1H, dd, *J* 8.15, 1.10 Hz), 7.88 (1H, ddd, *J* 8.0, 7.1, 1.2 Hz), 7.67 (1H, dt, *J* 7.8, 0.9 Hz), 6.28 (1H, q, *J* 7.2 Hz), 1.83 (3H, d, *J* 7.8 Hz); δ_C (150 MHz, $CDCl_3$) 161.7, 159.3, 150.7, 145.7, 134.3, 130.5, 128.2, 126.2, 124.2, 58.5, 18.3; HRMS: $[M+H]^+$, found: 215.2093. $C_{11}H_9N_3O_2$ requires: 215.2091.

*3.3.8. Imidazo[5,1-b]quinazoline-3,9-dione (**9**).* Compound **3** (0.01 mol) of 1.89 g was suspended in excess of trimethyl orthoformate (10 mL) and heated at 150 °C for 5 h. The reaction mixture was concentrated in vacuo, and the residue was diluted with 5% sodium hydroxide (20 mL) and extracted with chloroform (3×20 mL). The combined organic layers were washed with 5% acetic acid water solution (2×10 mL) and with water (2×10 mL), dried over sodium sulfate and then evaporated in vacuo. The crude solid was crystallized from ethanol to give 1.5 g (75%) of **9** as a colorless product, mp 154–157 °C. Found: C 60.28; H 2.52; N 21.22. $C_{10}H_5N_3O_2$ requires: C 60.31; H 2.53; N 21.10%; UV (EtOH): λ_{max} (log ε)=228 (4.45), 246 (4.38), 255 (4.25), 328 (3.98) nm; IR (KBr): ν_{max}=1668 (C=O), 1618 (C=N); δ_H (600 MHz, $CDCl_3$) 8.66 (1H, s) 8.18 (1H, dd, *J* 8.1, 1.1 Hz), 7.95 (1H, dd, *J* 8.1, 0.9 Hz), 7.87 (1H, ddd, *J* 8.0, 7.1, 1.2 Hz), 7.63 (1H, dt, *J* 7.8, 0.9 Hz); δ_C (150 MHz, $CDCl_3$) 162.4, 158.4, 151.9, 148.2, 144.8, 134.6, 131.4, 128.6, 126.3, 124.0; HRMS: $[M+H]^+$, found 199.1793. $C_{10}H_5N_3O_2$ requires: 199.1877.

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