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Amine substitution of quinazolinones leads to selective nanomolar AChE inhibitors with 'inverted' binding mode

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ABSTRACT

Selective and nanomolar acetylcholinesterase inhibitors were obtained by connecting tri- and tetracyclic quinazolinones—previously described as moderately active and unselective cholinesterase (ChE) inhibitors—via a hydroxyl group in *para* position to an anilinic nitrogen with different amines linked via a three carbon atom spacer. These tri- and tetracyclic quinazolinones containing different alicyclic ring sizes and connected to tertiary amines were docked to a high-resolution *h*AChE crystal structure to investigate the preferred binding mode in relation to results obtained by experimental structure–activity relationships. While the 'classical orientation' locating the heterocycle in the active site was rarely found, an alternative binding mode with the basic aliphatic amine in the active center ('inverted' orientation) was obtained for most compounds. Analyses of extended SARs based on this inverted binding mode are able to explain the compounds' binding affinities at AChE.

1. Introduction

Alzheimer's disease (AD) is a progressive, degenerative disorder of the brain and the most common form of dementia. With improvements in health care, longer life expectancy, and continued rise of the average age of the population, the prevalence of AD is projected to increase dramatically over the coming years. The global prevalence of dementia is estimated to be as high as 24 million, and is predicted to double every 20 years through to 2040.[1] The main symptoms associated with AD involve a decline in cognitive function and primarily memory loss. In the later stage of the disease language deficits, depression, agitation, mood disturbances and psychosis are often seen.[2] The etiology of AD is not completely understood; however, there are several diverse pathological factors such as amyloid-β (Aβ) deposits,[3] τ-protein (τ) aggregation,[4] oxidative stress,[5] and decreased levels of acetylcholine (ACh).[6]

According to the cholinergic hypothesis, AD's pathophysiology and especially its later stage development of cognitive deficits is associated with a loss of cholinergic neurotransmission with decreased levels of acetylcholine in the brain areas dealing with learning, memory, behavior and emotional responses. Symptomatic treatment of AD can be achieved by increasing synaptic levels of ACh in the brain by inhibiting the neurotransmitter degrading enzyme acetylcholinesterase (AChE), which is primarily responsible for its hydrolysis and termination of action. Therefore, acetylcholinesterase inhibitors (AChEIs) reached the pharmaceutical market and despite their purely symptomatic mode of action still represent the first-line treatment of AD. Although tacrine was the first of the cholinesterase inhibitors approved for the treatment of AD in 1993, its use has been largely abandoned because of a high incidence of side effects, mainly hepatotoxicity; nevertheless, there are efforts to counteract tacrine's liver toxicity using hybrid and co-drug molecules.[7–10] Three other acetylcholinesterase inhibitors (AChEIs) are in clinical use today: donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Razadyne®) are approved for mild to moderate AD.[11] AChEIs prevent the breakdown of ACh and therefore boost cholinergic neurotransmission in forebrain regions, which is thought to constitute their clinical benefits.

Numerous novel AChEIs have been described in recent years,[12] and especially natural products and alkaloids turned out as a valuable source of novel lead structures.[13–15] It has to be emphasized that the huge majority of novel compounds described—and this is especially true for natural products and natural lead structures–are only moderately active and compounds rarely reach inhibitory activities below the micromolar range.[12–15] Thus nanomolar inhibitors are still desirable and so is information of how to yield them from lead structures with lower inhibitory activities.

Quinazolines are fused heterocycles that are of considerable interest in medicinal chemistry because of the diverse range of

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0968-0896/

their biological properties.[16,17] The most important derivatives of quinazoline systems known so far are keto-quinazolines, also called quinazolinones.[18,19] The quinazolinone moiety is an important pharmacophore showing many types of pharmacological activities,[18] and the quinazolinones are considered to be 'privileged structures' for drug development.[20] The chemistry of 4-oxo compounds (4(3*H*)-quinazolinones) has received an increasing interest because of its biological significance. Derivatives of this system show antifungal,[21] antimicrobial,[22] anti-bacterial,[21] anti-inflammatory,[23] anticonvulsant,[24] and antiproliferative activities.[25] SARs of the quinazolinone ring system examined in various studies suggest position 6 suitable for connection to other moieties (Fig. 1).[18,26]

Our group had synthesized novel tri- and tetracyclic quinazolinones and their corresponding reduced analogs (quinazolines) as ChEIs derived from the naturally occurring alkaloids deoxyvasicinone **1**, dehydroevodiamine chloride **2**, and rutaecarpine **3** (Fig. 1).[27,28] Deoxyvasicinone **1** (a five-membered ring tricyclic quinazolinone) exhibited a moderate inhibitory activity towards AChE with an IC_{50} of 82.5 μM, the corresponding six membered-tricyclic quinazolinone (the alkaloid mackinazolinone) showed an IC_{50} (AChE) of 38.6 μM, and the seven membered-tricyclic quinazolinone showed an IC_{50} (AChE) of 279 μM.[29] Low basicity combined with very poor water solubility and poor to moderate inhibitory activities made structural modifications of the heterocycle necessary for further development.

Tri- and tetracyclic moieties served as a starting point for studies to synthesize a novel series of dual acting compounds as AChE inhibitors/H_3 receptor antagonists.[30] The quinazolinone scaffold shows a high similarity to the aromatic and/or heterocyclic parts of many known H_3 antagonist ligands. By bridging the phenolic heterocycle via an ether differently sized tertiary amines could be attached to the heterocycle. This was carried out because the piperidinylpropoxy phenyl structure represents the key pharmacophore of a whole class of H_3 antagonists.[31] It was found that the tricyclic basic heterocycle connected to a piperidine via a three carbon atom spacer (compound **4**; Fig. 1) was the most potent compound at both targets with K_i (*h*H_3) = 76.2 nM, IC_{50} (*h*AChE) = 33.9 nM, and IC_{50} (*ee*AChE) = 66.5 nM, respectively.[30]

In accordance with SARs on H_3 antagonists[32] reduced basicity of the heterocycle decreases H_3 affinity. This was indeed also the case for our quinazolinones, where H_3 affinities of quinazolinones are around 40 fold lower than the affinity of their corresponding totally reduced forms (reduction of the carbonyl group and the imine double bond).[30]

The dual-acting compounds also exhibit considerable inhibitory activities at butyrylcholinesterase. For the quinazolinones connected to tertiary amines and presented herein, a good to excellent selectivity over BChE was observed (cf. Table 2). Therefore, the peculiar selectivity both over H_3 as well as BChE combined with the high affinity at AChE prompted us to investigate the SARs of

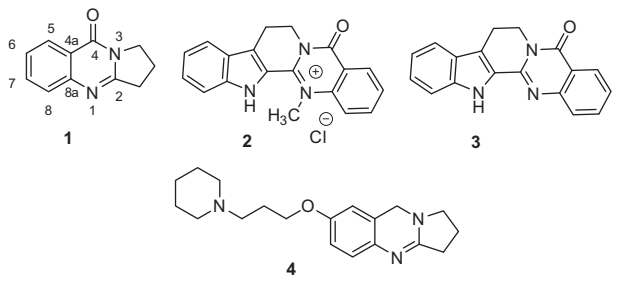


Figure 1. Chemical structures of deoxyvasicinone **1**, dehydroevodiamine chloride **2**, rutaecarpine **3** and dual-acting AChEI and *h*H_3 antagonist **4**.

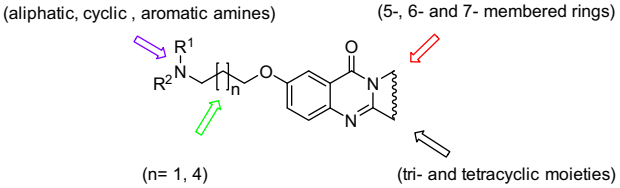


Figure 2. Structural modification on the quinazolinone moiety for structure-activity relationships.

this novel class of potent AChE inhibitors and to identify the putative binding mode at the molecular level for further compound development.

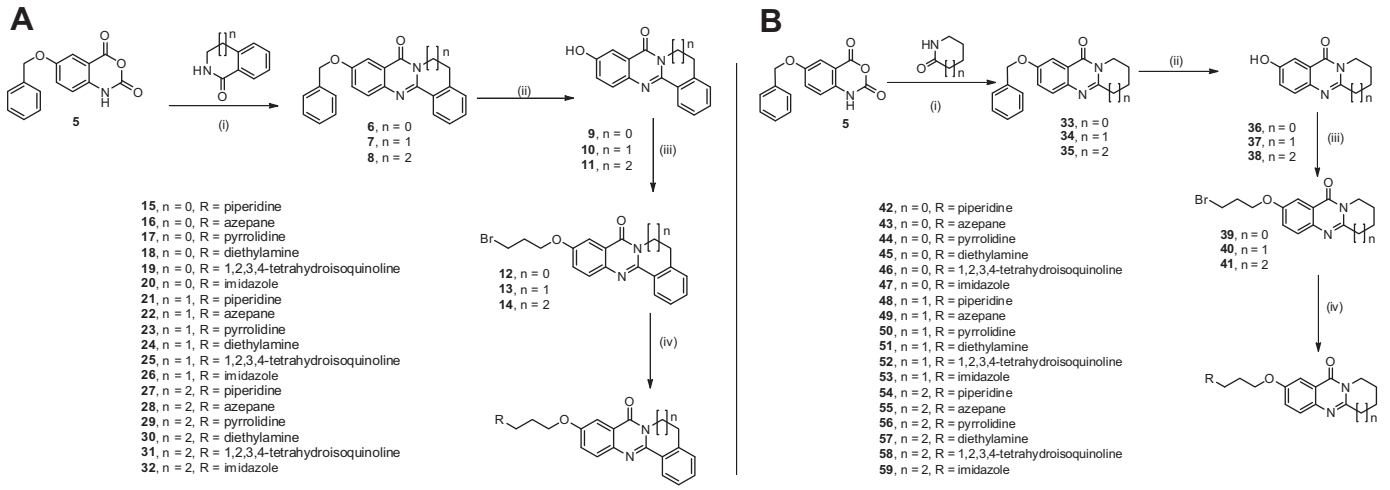
SAR studies (Fig. 2) have been performed on two different classes of heterocyclic compounds, that is, tri- and tetracyclic quinazolinones connected to various tertiary amines by different spacer lengths. For each moiety, firstly the effect of the nature of the connected amines was evaluated by connecting the phenolic quinazolinones with a cyclic amine such as pyrrolidine, piperidine, and azepane, with diethylamine as aliphatic amine, or 1,2,3,4-tetrahydroisoquinoline and imidazole as heterocyclic amines, respectively. Differences in inhibitory activity provide information on the role of this moiety with regards to molecular interaction with the enzyme. Secondly, the influence of the ring size of the quinazolinone's fused alicyclic ring was evaluated (five-, six-, seven-membered ring; tri- and tetracyclic fused systems). A putative correlation of SARs on the heterocycles of this class of compounds with the ones of unsubstituted quinazolinones and related heterocycles was investigated.[27,29] Thirdly, we also evaluated the influence of the spacer length between the phenolic heterocycle and the basic amine (three and six carbon atoms spacer length) (Fig. 2).[30]

According to a computational study by AbdulHameed et al.[33] on quinazolinimine-based BChEIs synthesized in our group, the core heterocycle of quinazolinones, quinazolines and quinazolinimines binds to the catalytic active site (CAS) at the end of the cholinesterase binding gorge. Herein, we assume that the quinazolinones connected to a tertiary amine as phenol ethers (i.e. amino-propoxy phenyl compounds) might not bind to the CAS in the 'classical' binding mode of quinazolinones, but with the tertiary amine being placed in or near the CAS, which will be referred to as an 'inverted' binding mode. An intensive computational study with all synthesized inhibitors was performed to investigate and understand the binding mode of these sets of compounds, and to provide feedback to experimentally prove this assumption by synthesizing additional inhibitors and provide further information for optimization of this novel class of AChE inhibitors.

2. Chemistry

A straightforward synthesis for 6-substituted quinazolinones was developed using 6-(benzyloxy)-1*H*-benzo[*d*][1,3]oxazine-2,4-dione **5** (Scheme 1) as starting material. It was synthesized in four steps starting from 2-amino-5-hydroxybenzoic acid with overall almost quantitative yield as previously described.[30,34] The resulting isatoic anhydride **5** represents an activated form of anthranilic acid with a benzyl protected phenolic OH. The benzylation of the phenolic group in compound **5** is very advantageous for subsequent synthetic steps by improvement of solubility of the resulting isatoic anhydride.

Tetracyclic compounds (Scheme 1A) were synthesized by solventless fusion of isoindolin-1-one, 3,4-dihydroisoquinolin-1(2*H*)-one or 2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-1-one, respectively, with compound **5** under microwave conditions with 200 W irradiation power at 220 °C for one hour to get the benzylated tetracyclic



Scheme 1. (A) Synthesis of tetracyclic quinazolinones, reagents and conditions: (i) MW, 200 W, 200 °C, 1 h; (ii) H_2, Pd/C, ethanol, rt, 24 h; (iii) 1,3-dibromopropane, K_2CO_3, KI, acetonitrile, 90 °C, 3 h; (iv) amine, K_2CO_3, KI, acetonitrile, 90 °C, 3 h. (B) Synthesis of tricyclic quinazolinones, reagents and conditions: (i) MW, 200 W, 200 °C, 1 h; (ii) H_2, Pd/C, ethanol, rt, 24 h; (iii) 1,3-dibromopropane, K_2CO_3, KI, acetonitrile, 90 °C, 3 h; (iv) amine, K_2CO_3, KI, acetonitrile, 90 °C, 3 h.

Table 1
*h*AChE inhibition results of selected tri- and tetracyclic compounds

Compd	*h*AChE inhibition [IC_{50} (pIC_{50} ± SEM)]	Compd	*h*AChE inhibition [IC_{50} (pIC_{50} ± SEM)]
Tacrine	71.5 nM (7.145 ± 0.038)	**42**	1.1 μM (5.966 ± 0.183)
15	142 nM (6.845 ± 0.144)	**45**	1.2 μM (5.905 ± 0.136)
18	200 nM (6.697 ± 0.11)	**48**	225 nM (6.648 ± 0.211)
21	216 nM (6.664 ± 0.085)	**51**	1.5 μM (5.815 ± 0.253)
24	669 nM (6.174 ± 0.149)	**54**	820 nM (6.086 ± 0.219)
27	535 nM (6.272 ± 0.087)	**57**	12.1 μM (4.918 ± 0.045)
30	4.2 μM (5.379 ± 0.338)	**61**	35% inhibition at 100 μM
32	56.5 μM (4.248 ± 0.167)		

compounds **6**, **7** and **8**, respectively, with different fused ring sizes. Quantitative debenzylation by catalytic hydrogenation over Pd/C in ethanol at room temperature gave the corresponding phenolic tetracyclic compounds **9**, **10** and **11**. Williamson ether synthesis by reaction of compounds **9**, **10** and **11** with 1,3-dibromopropane in presence of potassium carbonate as a base with a catalytic amount of potassium iodide in acetonitrile as solvent under reflux for three hours gave compounds **12**, **13**, and **14**, respectively. The last synthetic step was nucleophilic substitution by reaction of bromo compounds **12**, **13**, **14** with different secondary amines using the above alkylation conditions. The tetracyclic five-membered ring target compounds **15**–**20** were obtained by reaction of compound **12** with secondary amines (piperidine, azepane, pyrrolidine, diethylamine, 1,2,3,4-tetrahydroisoquinoline and imidazole). The tetracyclic six-membered ring target compounds **21**–**26** were obtained by reaction of compound **13** with the respective secondary amines, and tetracyclic seven-membered ring target compounds **27**–**32** by reaction of compound **14** (Scheme 1A).

Similarly, tricyclic compounds (Scheme 1B) were synthesized by solventless fusion of pyrrolidin-2-one, piperidin-2-one or azepan-2-one with compound **5** under microwave conditions to yield the benzylated tricyclic compounds **33**, **34** and **35**, respectively. Quantitative debenzylation by catalytic hydrogenation gave the corresponding phenolic tricyclic compounds **36**, **37**, **38**. Williamson ether synthesis under the same conditions described above gave compounds **39**, **40**, **41**, respectively. Tricyclic target compounds **42**–**59** were synthesized by nucleophilic substitution reaction of the bromo spacer compounds **39**, **40** and **41**, respectively, with the corresponding secondary amines using the same conditions described above for the tetracyclic target compounds (Scheme 1B).

3. AChE and BChE inhibition

All target compounds were tested for their ability to inhibit acetylcholinesterase (*ee*AChE, EC.3.1.1.7 from electric eel) and butyrylcholinesterase (*eq*BChE, EC.3.1.1.8 from equine serum) (Table 2) (cf. SI for sequence alignment).

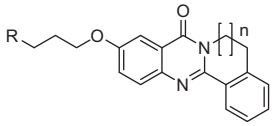
Additionally, selected compounds (quinazolinones with a piperidinyl, diethylamino or one imidazole substituent, respectively) were additionally tested for inhibition of human acetylcholinesterase (*h*AChE) to confirm binding profiles directly at the human enzyme (Table 1). It was found that tacrine shows a threefold lower potency (IC_{50} = 71.5 nM) on the human enzyme compared to the IC_{50} value of 24.1 nM measured on *ee*AChE. The piperidinyl inhibitors **15**, **21**, **27**, **42**, **48** and **54** showed 7 to 39 fold higher inhibitory activities toward the electric eel derived AChE (Tables 1 and 2). This difference in potency was not seen before for related nitrogen-bridgehead compounds and is not immediately plausible from the structural point of view due to highly conserved amino acids in the binding site of these two species.[30] A difference in inhibition data on these two AChEs from different species was previously also described for pyridonepezils and quinolinodonepezils and a set of tacrine dimers.[35,36]

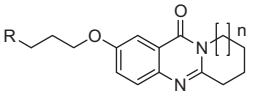
4. Computational binding mode analysis

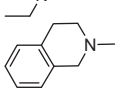
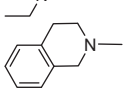
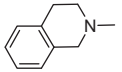
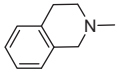
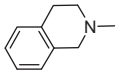
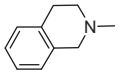
Docking studies were carried out to investigate whether the compounds of the inhibitor library show a common binding mode preference with respect to AChE. In principle, two different modes of inhibition are imaginable: first, a 'classical' binding mode corresponding to the placement of the tri- or tetracyclic scaffold near the catalytic active site (CAS), assumed for tri- and tetracyclic ChE inhibitors without an alkylamine, for example, unsubstituted quinazolinones (cf. Fig. 4); and, second, an inverted binding mode where instead of the aromatic scaffold the protonated tertiary amine is positioned at the CAS deep in the binding gorge. Interestingly, as further detailed below, docking shows a clear preference for the inverted binding mode for the vast majority of the library compounds: among the top-five docking poses obtained for each compound, inverted binding was observed in 77% (tricyclic compounds) and 99% (tetracyclic compounds) of the cases, respectively.

As shown in Figure 3 for inhibitor **15** as an example, the inverted binding mode is characterized by placement of the alicy-

Table 2
*ee*AChE and *eq*BChE inhibition results and the resulting ChE selectivity of tetra- and tricyclic target compounds





Compd	*n*	R	*ee*AChE[a] [IC_{50} (pIC_{50} ± SEM)]	*eq*BChE[a] [IC_{50} (pIC_{50} ± SEM)]	Selectivity[b]	Compd	*n*	R	*ee*AChE[a] [IC_{50} (pIC_{50} ± SEM)]	*eq*BChE[a] [IC_{50} (pIC_{50} ± SEM)]	Selectivity[b]
Tacrine			24.1 nM (7.619 ± 0.081)	3.7 nM (8.436 ± 0.012)	0.2						
15	0		6.9 nM (8.161 ± 0.03)	4.14 μM (3.383 ± 0.028)	600	**42**	0		69.2 nM (7.160 ± 0.152)	122 μM (3.912 ± 0.145)	1767
16	0		5.0 nM (8.305 ± 0.065)	1.87 μM (5.727 ± 0.069)	374	**43**	0		50.2 nM (7.299 ± 0.072)	5.22 μM (5.282 ± 0.024)	104
17	0		16.2 nM (7.790 ± 0.027)	2.40 μM (5.620 ± 0.007)	148	**44**	0		50.0 nM (7.301 ± 0.073)	10.55 μM (4.977 ± 0.039)	211
18	0		11.0 nM (7.961 ± 0.036)	1.88 μM (5.726 ± 0.145)	171	**45**	0		101 nM (6.997 ± 0.059)	829 nM (6.082 ± 0.066)	8
19	0		227 nM (6.644 ± 0.047)	1.73 μM (5.763 ± 0.043)	8	**46**	0		868 nM (6.062 ± 0.066)	776 nM (6.110 ± 0.053)	1
20	0		454 nM (6.343 ± 0.013)	9.11 μM (5.041 ± 0.06)	20	**47**	0		1.90 μM (5.721 ± 0.017)	14.65 μM (4.834 ± 0.040)	8
21	1		5.5 nM (8.263 ± 0.065)	955 nM (6.020 ± 0.051)	174	**48**	1		33.3 nM (7.478 ± 0.052)	6.55 μM (5.184 ± 0.028)	197
22	1		13.0 nM (7.886 ± 0.128)	584 nM (6.233 ± 0.021)	45	**49**	1		58.5 nM (7.233 ± 0.033)	1.77 μM (5.573 ± 0.021)	30
23	1		91.1 nM (7.041 ± 0.026)	955 nM (2.380 ± 0.008)	11	**50**	1		210 nM (6.679 ± 0.059)	16.08 μM (4.794 ± 0.013)	77
24	1		47.5 nM (7.323 ± 0.052)	2.16 μM (5.666 ± 0.047)	46	**51**	1		43.0 nM (7.367 ± 0.038)	9.14 μM (5.039 ± 0.015)	213
25	1		625 nM (6.204 ± 0.038)	1.83 μM (5.737 ± 0.051)	3	**52**	1		723 nM (6.141 ± 0.035)	5.49 μM (5.261 ± 0.024)	8
26	1		2.44 μM (5.613 ± 0.103)	8.68 μM (5.061 ± 0.092)	4	**53**	1		4.24 μM (5.373 ± 0.013)	50.05 μM (4.229 ± 0.035)	12
27	2		57.1 nM (7.244 ± 0.021)	2.67 μM (5.573 ± 0.027)	47	**54**	2		43.0 nM (7.366 ± 0.055)	12.73 μM (4.895 ± 0.032)	296
28	2		53.4 nM (7.272 ± 0.042)	865 nM (6.063 ± 0.017)	16	**55**	2		39.2 nM (7.407 ± 0.030)	1.80 μM (5.744 ± 0.048)	46
29	2		529 nM (6.277 ± 0.054)	3.61 μM (5.443 ± 0.021)	7	**56**	2		295 nM (6.531 ± 0.050)	12.19 μM (4.914 ± 0.067)	41
30	2		72.1 nM (7.142 ± 0.046)	5.10 μM (5.293 ± 0.024)	71	**57**	2		50.6 nM (7.296 ± 0.069)	10.75 μM (4.969 ± 0.059)	213
31	2		1.19 μM (5.925 ± 0.021)	1.84 μM (5.735 ± 0.032)	2	**58**	2		653 nM (6.185 ± 0.029)	3.03 μM (5.519 ± 0.067)	5
32	2		10.27 μM (4.989 ± 0.018)	52.01 μM (4.284 ± 0.045)	5	**59**	2		3.95 μM (5.403 ± 0.048)	59.75 μM (4.224 ± 0.086)	15
61	0		34% inhibition at. 50 μM	No inhibition at. 50 μM	–	**60**[30]	0		0.39 μM[30] (6.41 ± 0.05)	8.6 μM[30] (5.07 ± 0.01)	22

[a] AChE from electric eel and BChE from equine serum; data are the means of at least three independent determinations.
[b] Selectivity ratio [IC_{50} (BChE)/IC_{50} (AChE)].

clic amine at the CAS near Ser203 and His447 (*hAChE* numbering) and within cation–π-interaction distance to Trp86, a residue known for attracting the quaternary amine of the natural substrate acetylcholine.[37] The tetracyclic scaffold is sandwiched between Trp286 and Tyr341, showing ring-ring distances suitable for π–π interactions with Trp286, while the carboxamide carbonyl oxygen is stabilized by interactions with conserved water molecules. Analysis of the experimental SARs support this binding mode, as discussed in detail below.

5. Results and discussion

During our intensive SAR studies on the heterocyclic moiety we had been surprised to observe that connecting the tricyclic quinazolinone moiety with different cyclic amines by three carbon atom spacers improved AChE inhibition dramatically compared to the unsubstituted quinazolinones (Fig. 4).[30]

Different factors such as spacer length, the nature of the alicyclic amine, calculated pK_a values, synthesis of a carbocyclic analog of **15**, and docking studies helped to understand the characteristics of the amine-substituted quinazolinone class of compounds as AChE inhibitors and their putative binding mode.

The spacer length of three carbon atoms for the compounds of the inhibitor library was chosen on the basis of results obtained for heterocycles with dual-acting H_3 antagonist/AChE inhibiting properties.[30] To support the suitability of this choice, compound **60** was prepared as an analog of **42** with a six- instead of a three-carbon-atom spacer between the quinazolinone and the basic center. Compound **60** was found to be less active, with an IC_{50} (*ee*AChE) of 390 nM compared to 69.2 nM for **42** (Table 2).

The target compounds obtained by connection of tri- and tetracyclic quinazolinone moieties with different cyclic amines (pyrrolidine, piperidine, azepane) as basic center showed inhibition activity between one and three digit nanomolar IC_{50} values at *ee*AChE (from IC_{50} = 5.0 nM for compound **16** to 529 nM for compound **29**, cf. Table 2). Connection of the corresponding quinazolinones with diethylamine as basic center led to a similar inhibition range. In contrast, all target compounds from both tri- and tetracyclic quinazolinones with different fused ring sizes connected to 1,2,3,4-tetrahydroisoquinoline or imidazole showed only submicromolar to ten micromolar inhibition at AChE (from IC_{50} = 0.65
μM for compound **58** to 10.27 μM for compound **32**) (Table 2).

Interestingly, compounds with piperidine as amine substituent display the highest potency for AChE and, in particular, the best selectivity over BChE. The seven-membered ring compounds show activity in the same range, while the pyrrolidino compounds (with exception of compound **44**) have lower potencies, irrespective of the connected heterocycle. The fact that the nature of the connected tertiary amine has great influence on the inhibitory activity of the molecule (one to two digit nanomolar in case of aliphatic amine; submicromolar to two digit micromolar in case of imidazole or tetrahydroisoquinoline) is likely to be due to a binding mode in which the amine is placed in the CAS region.

Docking studies indeed point to an inverted binding mode as the clearly preferred orientation for the vast majority of the compounds. The notion of such an inverted binding mode is supported by various observations with respect to the experimental SARs: First of all, a positively charged tertiary amine is important for high-affinity binding. Compounds with a neutral imidazole substituent (pK_a = 7.07 based on a MoKa calculation[39]) show much weaker affinity. This can be interpreted in terms of an essential cation-π-interaction, most likely with Trp86 which is known to play a similar role in other AChE-complexes.[37,40]

The importance of amine basicity for potent AChE inhibition is reflected by a qualitative correlation with experimentally determined activity. Calculations with MoKa[39] provide the following pK_a values for the amine substituents: *N*,*N*-diethylamine 9.84, pyrrolidine 9.84, piperidine 9.71, azepane 9.58, 1,2,3,4-tetrahydroisoquinoline 8.68, and imidazole 7.07. These values correlate well with the pIC_{50} trends observed in homologous compound series (e.g., cf. the pIC_{50} values of the tricyclic compounds **42**–**47** with fused 6-membered ring: 7.00–7.30 with *N*,*N*-diethylamine, pyrrolidine, piperidine, or azepane as substituent; 6.06 with tetrahydroisoquinoline; and 5.72 with imidazole). Obviously, the influence of the basicity is modulated by steric factors determining the position of the charged amine with respect to the aromatic side chain to form cation–π interactions. While the small amines (pyrrolidine, piperidine, azepane, diethylamine) can all place their nitrogen at well-suited distances with respect to Trp86, steric hindrance prevents an optimal position in case of the 1,2,3,4-tetrahydroisoquinoline substituent (**19**, **25**, **31**, **46**, **52**, **58**), leading to less favorable interactions and weaker activity than expected on the basis of the amine basicity.

To provide further experimental evidence for the role of the basic center in the inverted binding mode, compound **61** was synthesized as carbon analog of compound **15** by replacing the piperidine by a cyclohexyl ring. Impressively, **61** loses most of the classes' inhibitory potency, showing only 34% inhibition of *ee*AChE at 50 μM, while compound **15** displays an IC_{50} (*ee*AChE) of 6.9 nM (Fig. 5). This dramatic activity difference strongly supports the essential role of the basic nitrogen, which can most plausibly be rationalized by a position at the CAS of AChE.

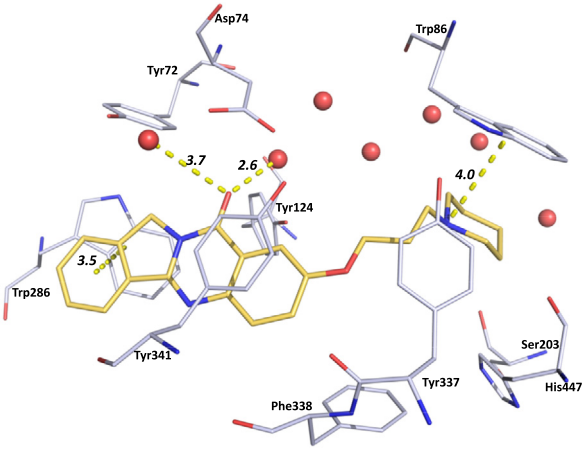


Figure 3. Inhibitor **15** is illustrated as an example of the smallest tetracyclic scaffold with the typical interactions found in the inverted binding mode: a 4.0 Å cation–π interaction with Trp86, a 2.6 Å hydrogen bond of the carboxamide carbonyl with water molecule 954, an additional 3.7 Å contact to water molecule 952, and a 3.5 Å π–π-interaction with Trp286. Distances are specified in Å as italic numbers. All figures showing docking poses were created with Pymol.[38]

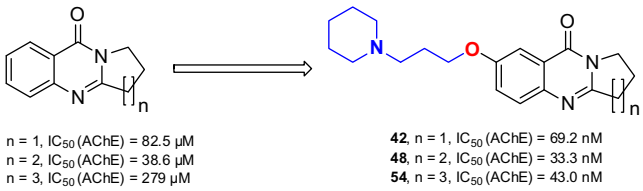


Figure 4. Acetylcholinesterase inhibitory activities of quinazolinones and their corresponding piperidinylpropoxy derivatives.[29,30]

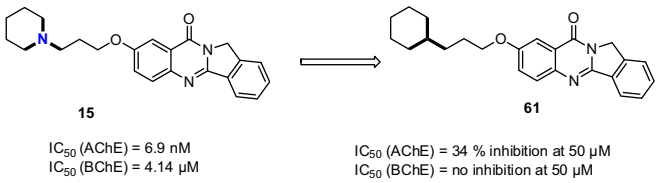


Figure 5. Effect of presence and absence of the basic center connected to the quinazolinone scaffold on AChE inhibitory activity.

Docking of compound **61** showed that, in principle, a binding mode as obtained for **15** may also be assumed for **61** (rms deviation: 0.90 Å), with the cyclohexyl ring located in the CAS region near Trp86. However, in comparison to **15** (score 103.06) compound **61** is scored much less favourably by GoldScore (score 92.20), pointing to the lack of the cation–π interaction and a considerably weaker affinity. While the other scoring functions available in GOLD besides GoldScore (ChemPLP, ASP, ChemScore)[41–46] were not able to reflect the affinity difference between the two compounds, the GoldScore values obtained for the docked poses of **15** and the other piperidinyl substituted compounds (**21**, **27**, **42**, **48**, **54**) in the inverted binding mode correlate very well ($R^2 = 0.92$) with the pIC_{50}, indicating that the modulation of the affinity by the different scaffolds is well captured by this scoring function and the binding mode obtained from docking (cf. SI Fig. 1).

For the tetracyclic scaffolds (**15**–**32**) a very clear preference for the inverted binding mode is found by docking. Within the top ten scored poses of each of these 18 inhibitors, the majority shows the inverted binding mode with cation–π interaction distances of 3.3–4.6 Å between the protonated alicyclic amine and Trp86, stabilization of the quinazolinone scaffold by water molecule 954 (cf. the Experimental part and SI Fig. 2 for details regarding the structural water molecules) and—in most of the cases—putative π–π interactions (3.2–3.5 Å) between the fused benzene moieties of the inhibitors and the indole side chain of Trp286 located at the entrance of the binding site. In more detail, inhibitors **15**–**20** with the smallest tetracyclic scaffold (corresponding to the most potent compounds of the library) show the carboxamide carbonyl pointing toward the water molecules, thus forming a 2.4 Å (**18**), 2.6 Å (**15**, **16**) and weak 3.5 Å (**19**, with an additional 2.9 Å interaction to water 952) hydrogen bond to water molecule 954 (cf. Fig. 3). Inhibitors **17** and **20** show a turned scaffold orientation in the binding pocket, forming a 2.9 Å and 2.8 Å interaction, respectively, between the scaffold nitrogen (instead of the carbonyl oxygen) and water molecule 954. This might contribute to their weaker inhibition potency compared to the other compounds of the same scaffold group.

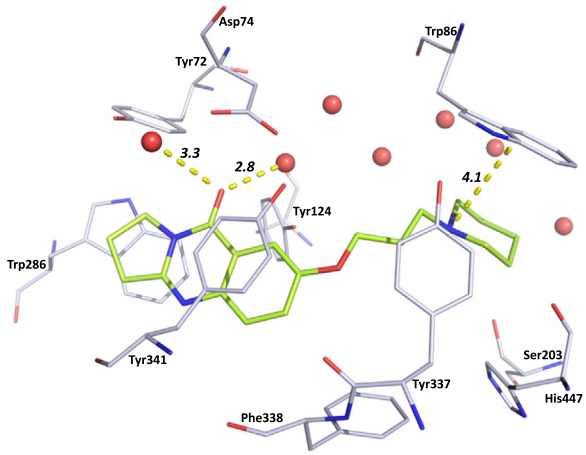


Figure 7. Inhibitor 42 is illustrated as an example of a compound with the smallest tricyclic scaffold and the inverted binding mode. The most important interactions consist of a 4.1 Å cation–π distance in the CAS region, a 2.8 Å distance of the carboxamide carbonyl oxygen to water molecule 954 and a hydrogen bridge of 3.3 Å to water molecule 952. Distances are specified in Å as italic numbers.

The hydrophobic interaction with Trp286 seen for most of the tetracyclic compounds (with exception of **18**, **20**, **25**, **28** and **31**) is in accordance with published distance preferences (3.4–3.6 Å),[47] supporting the assumption of a π–π interaction. With the sterically more demanding quinazolinones (with fused six- and seven-ring) this interaction seems to be particularly favored and shows best geometries in cases where the scaffold nitrogen instead of the carbonyl group is pointing to the water molecules (Fig. 6).

Also for the inhibitors with the tricyclic scaffolds **42**–**59** the inverted binding mode is preferred over the classical one (Fig. 7). Due to the smaller scaffold size compared to the one of the tetracycles, however, slightly more poses with the classical binding mode are found here. For the top-ten poses of the inhibitors bearing the azepane, pyrrolidine, or tetrahydroisoquinoline ring, the inverted binding mode is found exclusively. For the other inhibitors (**42**, **45**, **47**, **48**, **51**, **53**, **54**, **57**, **58** and **59**) between one and nine poses with the classical binding mode are found among the ten top-scoring poses.

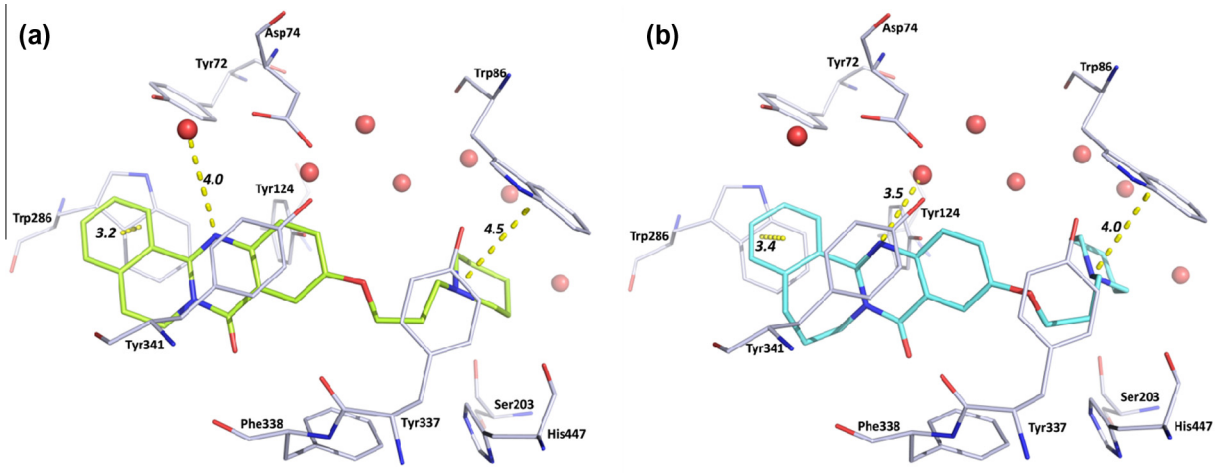


Figure 6. Due to the improved π–π interactions of the fused benzene and Trp286, the carboxamide carbonyl of the inhibitors **21** (**a**) and **27** (**b**) does not point to the water molecules, but to the opposite direction. Distances are specified in Å as italic numbers.

The chosen poses with inverted binding mode show a 2.5–3.1 Å distance of the carboxamide carbonyl oxygen to water molecule 954 and a 3.3–4.5 Å distance to water molecule 952, as shown exemplarily for ligand **42** in Figure 7. For the piperidine-, azepane- and pyrrolidine-rings the distance to Trp86 of the choline binding site varies only between 3.9 and 4.2 Å, whereas for the *N*,*N*-diethylamine substituent the observed distances range from 3.9 to 4.7 Å. Due to the bulkiness of the substituent, a close contact between the basic nitrogen and Trp86 is prevented for the tetrahydroisoquinoline-bearing inhibitors, possibly also explaining their comparatively weak inhibition potency (IC_{50}(*ee*AChE) from 653 to 868 nM).

6. Conclusion

The inhibitory activity and selectivity profile at AChE of previously described moderately active and unselective tri- and tetracyclic quinazolinones were dramatically improved by connecting them with different amines linked by three carbon atoms. Based on the experimental findings and the docking studies we assume that the inverted binding mode is preferred in terms of protein–ligand interactions. Besides cation–π and π–π interactions with Trp residues, structural water molecules can form hydrogen bonds with the ligand, especially with the carboxamide carbonyl oxygen, to mediate interactions with the AChE binding site.

Based on the affinity loss for the cyclohexyl-substituted inhibitor and the much weaker affinity for the (neutral) imidazole derivative compared to the corresponding piperidinyl analog, a protonated nitrogen is found to be essential for high affinity binding at the choline binding site. For the development of novel AChE inhibitors with a basic center it seems therefore crucial to investigate the putative binding mode by molecular docking and by SARs in order to be able to apply the most promising structural modifications to the inhibitors for further compound development.

7. Experimental part

7.1. Computational docking

Docking studies were performed with GOLD v5.1 and v5.2[48] following the previously described setup.[30] 50 docking poses were generated for each compound of the inhibitor library using the crystal structure 4EY7 of human AChE and seven conserved water molecules, as described in detail in a preceding study (cf. SI Fig. 1 for illustration of the hydrogen bond network formed by the water molecules in the AChE binding site). The protonation of the ligands (**15**–**32** and **42**–**59**) was set according to the expected ionization state at pH 8 (corresponding to the pH of the inhibition assay). This implied protonation at the tertiary amine for all compounds, consistent with their pK_a values between 8.68 and 9.84, as calculated with MoKa.[49] Based on a titration curve calculation, also performed with the program MoKa, the imidazole moiety is protonated to 10.6% and neutral to 89.4% at pH = 8. For the binding mode discussion only the predominant neutral form of the imidazole ring is considered. For the tricyclic inhibitors **54**–**59**, bearing a fused seven-membered alicycle, a conformational search was performed in MOE,[49] which resulted in six different conformational families (cf. SI Fig. 3). The MMFF94s force field was used and the conformers were generated in a stochastic search with 10,000 iterations and optimized to an rms gradient of 0.01 kcal/(mol Å). Each conformer was additionally locally minimized with the MMFF94x force field to an rms gradient of 0.001 kcal/(mol Å) for consistency with the general ligand setup.[30] All six conformers were docked with all of the tertiary amine moieties to the 4EY7 binding site. The conformer with a twist-like orientation of the seven membered ring proved to give consistent docking results of the ligand showing the inverted binding mode similar to the five- and six-membered ring analogs **42**–**53**.

As described in the Discussion, from the four scoring functions provided by GOLD, the GoldScore function[45,46] was chosen for the docking studies because it performed best with respect to relative affinity ranking. In all redocking experiments using GoldScore the top-ranked docking pose was deviating less than 0.91 Å from the corresponding crystal structure. All docking poses were clustered with a 1.5 Å cluster-cut-off by applying the complete linkage method.

In some cases not the absolute top pose of the inverted binding mode was chosen, but a pose displaying better hydrogen bond distances (2.6–3.0 Å) in agreement with experimentally observed preferences.[47] These poses vary on average by 0.91 score units and 1.33 Å with respect to the top pose, i.e. they belong to the same cluster. Distance measurements were carried out in Pymol.[38] For aromatic rings putatively involved in π–π or cation–π interactions the geometric centers were used for distance measurements.

7.2. Enzyme inhibition (acetyl- and butyrylcholinesterase inhibition assay)

AChE (E.C.3.1.1.7, Type VI-S, from Electric Eel) and BChE (E.C.3.1.1.8, from equine serum) were purchased from Sigma-Aldrich (Steinheim, Germany). DTNB (Ellman's reagent), ATC and BTC iodides were obtained from Fluka (Buchs, Switzerland). The assay was performed as described in the following procedure:[27,29] Stock solutions of the test compounds were prepared in ethanol, 100 μL of which gave a final concentration of 10^{-3} M when diluted to the final volume of 3.32 mL. The highest concentration of the test compounds applied in the assay was 10^{-4} M (10% EtOH in the stock solution did not influence enzyme activity). In order to obtain an inhibition curve, at least five different concentrations (normally 10^{-4}–10^{-9} M) of the test compound were measured at 25 °C and 412 nm, each concentration in triplicate. For buffer preparation, 1.36 g of potassium dihydrogen phosphate (10 mmol) were dissolved in 100 mL of water and adjusted with NaOH to pH = 8.0 ± 0.1. Enzyme solutions were prepared to give 2.5 units mL^{-1} in 1.4 mL aliquots. Furthermore, 0.01 M DTNB solution, 0.075 M ATC and BTC solutions, respectively, were used. A cuvette containing 3.0 mL of phosphate buffer, 100 μL of the respective enzyme, and 100 μL of the test compound solution was allowed to stand for 4.5 min, then 100 μL of DTNB were added, and the reaction was started by addition of 20 μL of the substrate solution (ATC/BTC). The solution was mixed immediately, and exactly 2.5 min after substrate addition the absorption was measured. For the reference value, 100 μL of water replaced the test compound solution. For determining the blank value, additionally 100 μL of water replaced the enzyme solution. The inhibition curve was obtained by plotting the percentage enzyme activity (100% for the reference) versus logarithm of test compound concentration. The same testing protocol was used for *h*AChE purchased from Sigma–Aldrich (Steinheim, Germany).

7.3. Chemistry

General methods

Common reagents and solvents were obtained from commercial suppliers and used without further purification. Reactions were conducted using dried flasks under a positive atmosphere of nitrogen. Reaction progress was monitored by analytical thin layer chromatography (TLC) on precoated silica gel GF254 plates. For detection iodine vapor, or UV light (254 nm), were used. Melting points are uncorrected and were measured in open capillary tubes, using a Barnstead Electrothermal IA9100 melting point apparatus. ^{1}H and ^{13}C NMR spectral data were obtained from a Bruker

Advance spectrometer (300 MHz and 75 MHz, respectively). Chemical shifts are expressed in ppm relative to $CDCl_3$ or DMSO-d_6 (7.26:2.50 and 77.16:39.52 ppm for ^1H and ^{13}C NMR, respectively). ESI-MS samples were analyzed using electrospray ionisation ion-trap mass spectrometry in nanospray mode using a Thermo Finnigan LCQ Deca. The CHN analyses were undertaken using Perkin Elmer Elemental Analyser PE2400CHNS. In the elemental analysis, small amounts of solvent were taken into account which had been applied in previous column chromatography or for transferring the compounds to another vessel. For column chromatography, silica gel 60, 230–400 mesh (Merck) was used.

6-(Benzyloxy)-1*H*-benzo[*d*][1,3]oxazine-2,4-dione **5** was synthesized in four steps with almost quantitative overall yield, starting from 2-amino-5-hydroxybenzoic acid.[30,34]

7.3.1. General synthetic procedure (I) for compounds 6, 7, 8, 33, 34 and 35

The respective lactame or benzolactame and 6-benzyloxyisatoic anhydride **5** were placed in a 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. The sealed reaction tube was placed inside the cavity of a CEM Discover focused microwave synthesis system, operated at 200 °C (temperature monitored by a built-in infrared sensor), power 200 W, for 1 h. The residue was purified by column chromatography using dichloromethane/methanol (20:1) as eluent system to afford the title compounds.

7.3.2. 8-(Benzyloxy)isoindolo[1,2-*b*]quinazolin-10(12*H*)-on (6)

Starting from isoindolin-1-one (410 mg, 3.4 mmol) and 6-benzyloxyisatoic anhydride **5** (915 mg, 3.4 mmol).The title compound was obtained as a beige solid (740 mg, 64% yield). Mp = 161–163 °C. R_t: 2.938 min, HRESIMS ($C_{22}H_{16}N_2O_2$+H)$^+$, *m*/*z* calcd: 342. 1245; found: 342.1286. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.23 (d, J = 6.7 Hz, 1H), 7.90–7.78 (m, 2H), 7.70–7.55 (m, 3H), 7.53–7.33 (m, 7H), 5.21 (s, 2H), 5.18 (s, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.94, 154.33, 151.29, 132.93, 132.91, 132.23, 132.00, 131.40, 130.59, 129.62, 129.02, 128.70, 128.25, 127.74, 126.25, 125.09, 123.52, 107.32, 70.58, 49.91 ppm.

7.3.3. 10-(Benzyloxy)-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (7)

Starting from 3,4-dihydroisoquinolin-1(2*H*)-one (0.5 g, 3.4 mmol) and 6-benzyloxyisatoic anhydride **5** (915 mg, 3.4 mmol). The title compound was obtained as a beige solid (870 mg, 72% yield). Mp = 157–159 °C. R_t: 3.393 min, HRESIMS ($C_{23}H_{18}N_2O_2$+H)$^+$, *m*/*z* calcd: 355.1402; found: 355.1441. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.45 (d, J = 7.9 Hz, 1H), 7.78 (d, J = 2.9 Hz, 1H), 7.74 (d, J = 8.9 Hz, 1H), 7.53–7.26 (m, 9H), 5.19 (s, 2H), 4.51–4.36 (m, 2H), 3.20–3.00 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.49, 157.45, 147.54, 136.74, 136.37, 131.42, 129.31, 128.68, 128.21, 127.75, 127.72, 127.65, 127.51, 125.18, 121.46, 107.40, 70.53, 39.78, 27.53 ppm.

7.3.4. 11-(Benzyloxy)-6,7-dihydrobenzo[3,4]azepino[2,1-*b*]quinazolin-9(5*H*)-one (8)

Starting from 2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-1-one (0.55 g, 3.4 mmol) and 6-benzyloxyisatoic anhydride **5** (915 mg, 3.4 mmol). The title compound was obtained as a yellow thick oil (750 mg, 60% yield). R_t: 3.298 min, HRESIMS ($C_{24}H_{20}N_2O_2$+H)$^+$, *m*/*z* calcd: 369.1603; found: 369.1610. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.90–7.82 (m, 1H), 7.80 (d, J = 2.9 Hz, 1H), 7.73 (d, J = 8.9 Hz, 1H), 7.53–7.29 (m, 9H), 7.22 (dd, J = 12.2, 10.8 Hz, 1H), 5.20 (s, 2H), 4.97–3.18 (m, 2H), 2.76 (t, J = 7.1 Hz, 2H), 2.48–2.06 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.46, 157.56, 154.39, 142.62, 137.92, 136.35, 134.96, 131.11, 129.34, 128.95, 128.69, 128.61, 128.22, 127.70, 127.48, 125.13, 121.20, 107.36, 70.53, 41.59, 29.78, 28.79 ppm.

7.3.5. 7-(Benzyloxy)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (33)

Starting from pyrrolidin-2-one (1.00 g, 12.25 mmol) and 6-benzyloxyisatoic anhydride **5** (1.00 g, 3.71 mmol). The title compound was obtained as a yellow solid (450 mg, 78% yield). Mp 188–190 °C. ESI-MS: 293.0 *m*/*z* [MH]$^+$. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.75 (d, J = 2.9 Hz, 1H), 7.65–7.58 (m, 1H,), 7.47 (dd, J = 8.2, 1.2 Hz, 1H), 7.44–7.29 (m, 5H), 5.17 (s, 2H), 4.30–4.11 (m, 2H), 3.25–3.08 (m, 2H), 2.39–2.20 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.76, 157.41, 157.18, 149.10136.34, 131.25, 128.66, 128.24, 128.20, 127.71, 124.90, 107.14, 70.51, 46.57, 32.25, 19.69 ppm.

7.3.6. 2-(Benzyloxy)-8,9-dihydro-6*H*-pyrido[2,1-*b*]quinazolin-11(7*H*)-one (34)

Starting from piperidin-2-one (1.11 g, 11.17 mmol) and 6-benzyloxyisatoic anhydride **5** (1.50 g, 5.58 mmol). The title compound was obtained as a yellow oil (900 mg, 80% yield). R_t: 2.314 min, HRESIMS ($C_{19}H_{18}N_2O_2$+H)$^+$, *m*/*z* calcd: 307.1402; found: 307.1458. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.69 (d, J = 2.9 Hz, 1H), 7.52 (t, J = 6.8 Hz, 1H), 7.47–7.41 (m, 2H), 7.41–7.27 (m, 4H), 5.13 (s, 2H), 4.04 (t, J = 6.2 Hz, 2H), 2.94 (t, J = 6.6 Hz, 2H), 2.11–1.77 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.98, 156.93, 152.64, 142.22, 136.42, 128.63, 128.14, 128.08, 127.67, 125.10, 121.04, 107.02, 70.43, 42.44, 31.75, 22.15, 19.39 ppm.

7.3.7. 2-(Benzyloxy)-7,8,9,10-tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one (35)

Starting from azepan-2-one (1.26 g, 11.17 mmol) and 6-benzyloxyisatoic anhydride **5** (1.50 g, 5.58 mmol). The title compound was obtained as a yellow solid (900 mg, 80% yield). Mp = 127–128 °C. R_t: 2.683 min, HRESIMS ($C_{20}H_{20}N_2O_2$+H)$^+$, *m*/*z* calcd: 321.1603; found: 321.1602. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.69 (d, J = 2.9 Hz, 1H), 7.52 (t, J = 6.9 Hz, 1H), 7.49–7.41 (m, 2H), 7.41–7.27 (m, 4H), 5.13 (s, 2H), 4.36 (d, J = 5.5 Hz, 2H), 3.15–2.88 (m, 2H), 1.82 (d, J = 4.1 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.74, 157.55, 157.19, 142.16, 136.41, 128.64, 128.43, 128.15, 127.66, 124.94, 120.90, 107.57, 70.44, 42.98, 37.52, 29.58, 28.14, 25.53 ppm.

7.3.8. General synthetic procedure (II) for compounds 9, 10, 11, 36–38

To a mixture of the benzylated quinazolinones and 10% Pd-C ethanol was added. The mixture was stirred at room temperature and under an atmosphere of H_2 for 4 h. The mixture then was filtered over celit and then the solvent removed under reduced pressure to afford the title phenolic compounds.

7.3.9. 8-Hydroxyisoindolo[1,2-*b*]quinazolin-10(12*H*)-one (9)

Starting from 8-(benzyloxy)isoindolo[1,2-*b*]quinazolin-10(12*H*)-one **6** (700 mg, 2.06 mmol) and 10% Pd-C (80 mg). The title compound was obtained as a yellow solid (450 mg, 87%). Mp = 306–308 °C. R_t: 1.72 min, HRESIMS ($C_{15}H_{10}N_2O_2$+H)$^+$, *m*/*z* calcd: 251.0776; found: 251.0815. ^1H NMR (300 MHz, DMSO) δ: 10.12 (s, 1H), 8.03 (d, J = 7.5 Hz, 1H), 7.74 (t, J = 6.7 Hz, 1H), 7.72–7.63 (m, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 5.2 Hz, 1H), 7.31 (dd, J = 8.8, 2.9 Hz, 1H), 5.14 (s, 2H) ppm. ^{13}C NMR (75 MHz, DMSO) δ: 159.17, 155.85, 152.14, 142.10, 139.94, 132.28, 131.67, 128.68, 128.49, 123.98, 123.55, 122.23, 121.27, 108.78, 49.58 ppm.

7.3.10. 10-Hydroxy-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (10)

Starting from 10-(benzyloxy)-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one **7** (800 mg, 2.26 mmol) and 10% Pd-C (80 mg). The title compound was obtained as a yellow solid (530 mg, 89%). Mp = 255–257 °C. ESI-MS: 264.7 *m*/*z* [M]$^+$. ^1H NMR (400 MHz,

DMSO) δ: 10.03 (s, 1H), 8.31 (dd, J = 7.8, 1.2 Hz, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.45 (m, 4H), 7.30 (dd, J = 8.8, 2.9 Hz, 1H), 4.36–4.18 (m, 2H), 3.09 (t, J = 6.4 Hz, 2H) ppm. ^{13}C NMR (101 MHz, DMSO) δ: 160.18, 156.08, 146.27, 140.43, 137.10, 131.04, 129.23, 128.97, 127.63, 127.02, 126.82, 123.90, 121.31, 109.03, 39.15, 26.44 ppm.

7.3.11. 11-Hydroxy-6,7-dihydrobenzo[3,4]azepino[2,1-*b*]quinazolin-9(5*H*)-one (11)

Starting from 11-(benzyloxy)-6,7-dihydrobenzo[3,4]azepino[2,1-*b*]quinazolin-9(5*H*)-one **8** (700 mg, 1.9 mmol) and 10% Pd-C (80 mg). The title compound was obtained as a yellow solid (470 mg, 89%). Mp = 257–259 °C. R_t: 2.015 min, HRESIMS ($C_{17}H_{14}N_2O_2$+H)$^+$, m/z calcd: 279.1128; found: 279.1127. ^{1}H NMR (300 MHz, DMSO) δ: 10.16 (s, 1H), 7.75 (dd, J = 7.4, 1.2 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.55–7.38 (m, 3H), 7.37–7.25 (m, 2H), 3.92 (s, 2H), 2.70 (t, J = 6.5 Hz, 2H), 2.18–2.07 (m, 2H) ppm. ^{13}C NMR (75 MHz, DMSO) δ: 159.14, 155.16, 151.83, 139.56, 136.54, 133.67, 129.62, 127.97, 127.67, 127.40, 125.74, 122.76, 119.86, 107.90, 39.84, 27.81, 27.01 ppm.

7.3.12. 7-Hydroxy-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (36)

Starting from 7-(benzyloxy)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one **33** (750 mg, 2.57 mmol) and 10% Pd-C (80 mg). The title compound was obtained as a beige solid (450 mg, 87% yield). Mp = 284–287 °C. ^{1}H NMR (300 MHz, DMSO) δ: 9.95 (s, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 2.8 Hz, 1H), 7.23 (dd, J = 8.8, 2.9 Hz, 1H,), 4.12–3.94 (m, 2H), 3.08–2.94 (m, 2H), 2.21–2.10 (m, 2H) ppm.

7.3.13. 2-Hydroxy-8,9-dihydro-6*H*-pyrido[2,1-*b*]quinazolin-11(7*H*)-one (37)

Starting from 2-(benzyloxy)-8,9-dihydro-6*H*-pyrido[2,1-*b*]quinazolin-11(7*H*)-one **34** (750 mg, 2.45 mmol) and 10% Pd-C (80 mg). The title compound was obtained as a beige solid (430 mg, 81%). Mp = 252–253 °C. R_t: 0.957 min, HRESIMS ($C_{12}H_{12}N_2O_2$+H)$^+$, m/z calcd: 217.0932; found: 217.0973. ^{1}H NMR (300 MHz, DMSO) δ: 10.04 (s, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 2.8 Hz, 1H), 7.25 (dd, J = 8.8, 2.9 Hz, 1H), 3.92 (t, J = 6.1 Hz, 2H), 2.88 (t, J = 6.6 Hz, 2H), 2.00–1.74 (m, 4H) ppm. ^{13}C NMR (75 MHz, DMSO) δ: 160.52, 155.47, 152.63, 127.00, 123.89, 120.52, 108.63, 79.08, 41.71, 30.47, 21.28, 18.40 ppm.

7.3.14. 2-Hydroxy-7,8,9,10-tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one (38)

Starting from 2-(benzyloxy)-7,8,9,10-tetrahydroazepino[2,1-*b*]-quinazolin-12(6*H*)-one **35** (700 mg, 3.04 mmol) and 10% Pd-C (80 mg). The title compound was obtained as a beige solid (430 mg, 81%). Mp = 249–251 °C. R_t: 1.268 min, HRESIMS ($C_{13}H_{14}N_2O_2$+H)$^+$, m/z calcd: 231.1128; found: 231.1133. ^{1}H NMR (400 MHz, DMSO) δ: 9.97 (s, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.38 (d, J = 2.8 Hz, 1H), 7.22 (dd, J = 8.8, 2.9 Hz, 1H), 4.39–4.20 (m, 2H), 3.01 (dd, J = 13.6, 5.9 Hz, 2H), 1.83–1.60 (m, 6H) ppm. ^{13}C NMR (101 MHz, DMSO) δ: 160.62, 156.60, 155.68, 140.42, 128.16, 123.60, 120.51, 109.04, 41.83, 36.32, 28.69, 27.61, 25.01 ppm.

7.3.15. General synthetic procedure (III) for compounds 12, 13, 14, 39, 40 and 41

A mixture of 1,3-dibromopropane, free phenolic quinazolinone, potassium carbonate, and catalytic amount of potassium iodide were refluxed in absolute acetonitrile for 2 h. After cooling the inorganic salts were filtered off and the filtrate was concentrated under reduced pressure. The remaining residue was taken up in brine, and extracted with methylene chloride. The combined organic extracts were washed with brine and dried over magnesium sulfate. The organic solvent was removed under reduced pressure. The resulting crude product was purified by column chromatography using dichloromethane/methanol (30:1) as eluent system to afford the title compounds.

7.3.16. 8-(3-Bromopropoxy)isoindolo[1,2-*b*]quinazolin-10(12*H*)-one (12)

Starting from 1,3-dibromopropane (810 mg, 4.0 mmol), 8-hydroxyisoindolo[1,2-*b*]quinazolin-10(12*H*)-one **9** (400 mg, 1.60 mmol), potassium carbonate (415 mg, 3.0 mmol), and catalytic amount of potassium iodide. The title compound was obtained as a yellow solid (440 mg, 74%). Mp = 133–134 °C. ESI-MS: 372.8 m/z [M]$^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.12 (dd, J = 10.4, 4.5 Hz, 1H), 7.80–7.70 (m, 2H), 7.67–7.51 (m, 3H), 7.40–7.32 (m, 1H), 5.13 (s, 2H), 4.31–4.07 (m, 2H), 3.76–3.27 (m, 2H), 2.47–2.21 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.15, 154.97, 150.91, 141.82, 137.00, 130.50, 129.74, 126.72, 126.63, 122.34, 121.23, 120.96, 119.08, 104.61, 63.64, 47.56, 29.97, 27.59 ppm.

7.3.17. 10-(3-Bromopropoxy)-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (13)

Starting from 1,3-dibromopropane (810 mg, 4.0 mmol), 10-hydroxy-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one **10** (500 mg, 1.89 mmol), potassium carbonate (415 mg, 3.0 mmol), and catalytic amount of potassium iodide. The title compound was obtained as a yellow solid (550 mg, 76%). Mp = 136–138 °C. R_t: 3.278 min, HRESIMS ($C_{19}H_{17}BrN_2O_2$+H)$^+$, m/z calcd: 385.0552; found: 385.0541. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.54–8.39 (m, 1H), 7.79–7.65 (m, 2H), 7.51–7.40 (m, 2H), 7.36 (dd, J = 8.9, 2.9 Hz, 1H), 7.32–7.26 (m, 1H), 4.50–4.38 (m, 2H), 4.22 (m, 2H), 3.28 (m, 2H), 3.11 (t, J = 6.4 Hz, 2H), 2.43–2.28 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.96, 149.70, 147.64, 143.69, 140.25, 137.83, 136.78, 131.56, 129.16, 127.84, 127.70, 127.54, 124.91, 107.07, 67.50, 39.81, 32.84, 27.51, 6.36 ppm.

7.3.18. 11-(3-Bromopropoxy)-6,7-dihydrobenzo[3,4]azepino[2,1-*b*]quinazolin-9(5*H*)-one (14)

Starting from 1,3-dibromopropane (810 mg, 4.0 mmol), 11-hydroxy-6,7-dihydrobenzo[3,4]azepino[2,1-*b*]quinazolin-9(5*H*)-one **11** (555 mg, 2.0 mmol), potassium carbonate (415 mg, 3.0 mmol), and catalytic amount of potassium iodide. The title compound was obtained as a beige solid (600 mg, 75%). Mp = 138–140 °C. R_t: 3.184 min, HRESIMS ($C_{20}H_{19}BrN_2O_2$+H)$^+$, m/z calcd: 399.0703; found: 399.0696. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.91–7.81 (m, 1H), 7.76–7.65 (m, 2H), 7.52–7.32 (m, 3H), 7.24 (d, J = 1.3 Hz, 1H), 4.27 (m, 2H), 3.53 (m, 2H), 3.36 (m, 2H), 2.76 (t, J = 7.1 Hz, 2H), 2.26 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.33, 157.18, 152.63, 140.36, 138.44, 136.67, 129.73, 128.02, 127.30, 127.11, 126.75, 121.86, 119.06, 108.41, 41.60, 35.88, 35.38, 29.79, 28.78, 6.35 ppm.

7.3.19. 7-(3-Bromopropoxy)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (39)

Starting from 1,3-dibromopropane (810 mg, 4.0 mmol), 7-hydroxy-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one **36** (400 mg, 2.0 mmol), potassium carbonate (415 mg, 3.0 mmol), and catalytic amount of potassium iodide. The title compound was obtained as a yellow thick oil (430 mg, 67%). R_t: 2.135 min, HRESIMS ($C_{14}H_{15}BrN_2O_2$+H)$^+$, m/z calcd: 323.0390; found: 323.0392. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55 (d, J = 2.5 Hz, 1H), 7.49 (dd, J = 8.9, 1.4 Hz, 1H), 7.29–7.16 (m, 1H), 4.23–4.02 (m, 4H), 3.66–3.47 (m, 2H), 3.08 (t, J = 7.9 Hz, 2H), 2.36–2.24 (m, 2H), 1.97 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.71, 157.41, 156.96, 143.67, 128.20, 124.38, 121.12, 106.71, 65.81, 46.50, 32.16, 32.14, 29.82, 19.59 ppm.

7.3.20. 2-(3-Bromopropoxy)-8,9-dihydro-6*H*-pyrido[2,1-*b*]quinazolin-11(7*H*)-one (40)

Starting from 1,3-dibromopropane (480 mg, 2.37 mmol), 2-hydroxy-8,9-dihydro-6*H*-pyrido[2,1-*b*]quinazolin-11(7*H*)-one **37** (400 mg, 1.19 mmol), potassium carbonate (415 mg, 3.0 mmol), and catalytic amount of potassium iodide. The title compound was obtained as a beige solid (500 mg, 63%). Mp = 133–134 °C. R_t: 2.133 min, HRESIMS ($C_{15}H_{17}BrN_2O_2$+H)$^+$, *m*/*z* calcd: 337.0552; found: 337.0548. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.63 (d, *J* = 2.9 Hz, 1H), 7.55 (d, *J* = 8.9 Hz, 1H), 7.35–7.27 (m, 1H), 4.18 (m, 2H), 4.09 (t, *J* = 6.2 Hz, 2H), 3.69–3.33 (m, 2H), 2.99 (t, *J* = 6.6 Hz, 2H), 2.48–2.24 (m, 2H), 2.10–1.87 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.93, 156.42, 155.87, 128.00, 125.35, 124.86, 124.31, 106.69, 65.85, 42.51, 32.23, 31.73, 29.82, 22.17, 19.38 ppm.

7.3.21. 2-(3-Bromopropoxy)-7,8,9,10-tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one (41)

Starting from 1,3-dibromopropane (480 mg, 2.37 mmol), 2-hydroxy-7,8,9,10-tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one **38** (300 mg, 1.30 mmol), potassium carbonate (415 mg, 3.0 mmol), and catalytic amount of potassium iodide. The title compound was obtained as a beige solid (340 mg, 74%). Mp = 137–139 °C. R_t: 2.532 min, HRESIMS ($C_{16}H_{19}BrN_2O_2$+H)$^+$, *m*/*z* calcd: 351.0703; found: 351.0706. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.61 (dd, *J* = 10.6, 5.9 Hz, 2H), 7.36–7.28 (m, 1H), 4.41 (d, *J* = 5.5 Hz, 2H), 4.18 (m, 2H), 3.71–3.55 (m, 2H), 3.08 (d, *J* = 6.4 Hz, 2H), 2.47–2.26 (m, 2H), 1.97–1.75 (m, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.77, 157.61, 157.16, 128.40, 124.67, 122.75, 120.22, 107.22, 65.88, 43.11, 32.77, 32.19, 29.79, 29.57, 28.09, 25.48 ppm.

7.3.22. General synthetic procedure (IV) of 3-substituted quinazolinones

The corresponding amine, 3-bromopropoxy quinazolinone, potassium carbonate, and catalytic amount of potassium iodide were refluxed in absolute acetonitrile for 3 h. After cooling the inorganic salts were filtered off and the filtrate was concentrated under reduced pressure. The remaining residue was taken up in aq solution of NaCl, and extracted with methylene chloride. The combined organic extracts were washed with brine and dried over magnesium sulfate. The organic solvent was removed under reduced pressure. The resulting crude product was purified by column chromatography using dichloromethane/methanol (15:1) as eluent system to afford the corresponding target compounds:

7.3.23. 8-(3-(Piperidin-1-yl)propoxy)isoindolo[1,2-*b*]quinazolin-10(12*H*)-one (15)

Starting from 8-(3-bromopropoxy)isoindolo[1,2-*b*]quinazolin-10(12*H*)-one **12** (230 mg, 0.62 mmol) and piperidine (80 mg, 0.93 mmol). The title compound was obtained as beige solid (105 mg, 45%). Mp = 193–196 °C. R_t: 1.555 min, HRESIMS ($C_{23}H_{25}N_3O_2$+H)$^+$, *m*/*z* calcd: 376.202; found: 376.2029. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.18–8.09 (m, 1H), 7.74 (dd, *J* = 5.9, 4.5 Hz, 2H), 7.66–7.52 (m, 3H), 7.38 (dd, *J* = 8.9, 3.0 Hz, 1H), 5.15 (s, 2H), 4.13 (q, *J* = 6.7 Hz, 2H), 2.50 (dd, *J* = 21.3, 13.5 Hz, 6H), 2.15–1.95 (m, 2H), 1.61 (m, 4H), 1.53–1.37 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.51, 157.67, 153.02, 143.91, 139.24, 132.87, 131.93, 128.89, 128.88, 124.74, 123.50, 123.18, 121.37, 106.80, 67.15, 55.96, 54.67, 49.80, 26.72, 25.92, 24.41 ppm. Elem. Anal. ($C_{23}H_{25}N_3O_2 \times 0.06 \cdot CH_2Cl_2$) calcd: C, 72.78; H, 6.65; Cl, 1.12; N, 11.04; O, 8.41 found: C, 73.02; H, 6.66; N, 10.85.

7.3.24. 8-(3-(Azepan-1-yl)propoxy)isoindolo[1,2-*b*]quinazolin-10(12*H*)-one (16)

Starting from 8-(3-bromopropoxy)isoindolo[1,2-*b*]quinazolin-10(12*H*)-one **12** (230 mg, 0.62 mmol) and azepane (90 mg, 0.93 mmol). The title compound was obtained as a beige solid (115 mg, 48%). Mp = 145–148 °C. R_t: 1.63 min, HRESIMS ($C_{24}H_{27}N_3O_2$+H)$^+$, *m*/*z* calcd: 390.2176; found: 390.2175. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.13 (dd, *J* = 10.4, 4.7 Hz, 1H), 7.74 (t, *J* = 6.0 Hz, 2H), 7.58 (m, 3H), 7.37 (dd, *J* = 8.9, 3.0 Hz, 1H), 5.15 (s, 2H), 4.16 (t, *J* = 6.2 Hz, 2H), 2.93–2.70 (m, 6H), 2.21–2.03 (m, 2H), 1.83–1.54 (m, 8H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.50, 157.55, 153.08, 143.97, 139.24, 132.85, 131.96, 128.94, 128.89, 124.61, 123.51, 123.20, 121.38, 106.93, 66.77, 55.40, 54.76, 49.80, 27.20, 27.01, 26.87 ppm. Elem. Anal. ($C_{24}H_{27}N_3O_2 \times 0.5 \cdot CH_2Cl_2$) calcd: C, 68.12; H, 6.53; Cl, 8.21; N, 9.73; O, 7.41 found: C, 68.10; H, 6.67; N, 9.65.

7.3.25. 8-(3-(Pyrrolidin-1-yl)propoxy)isoindolo[1,2-*b*]quinazolin-10(12*H*)-one (17)

Starting from 8-(3-bromopropoxy)isoindolo[1,2-*b*]quinazolin-10(12*H*)-one **12** (230 mg, 0.62 mmol) and pyrrolidine (66 mg, 0.93 mmol). The title compound was obtained as beige solid (100 mg, 45%). Mp = 234–236 °C. R_t: 1.47 min, HRESIMS ($C_{22}H_{23}N_3O_2$+H)$^+$, *m*/*z* calcd: 362.1863; found: 362.1862. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.13 (dd, *J* = 10.2, 4.6 Hz, 1H), 7.80–7.70 (m, 2H), 7.66–7.52 (m, 3H), 7.38 (dd, *J* = 9.0, 2.9 Hz, 1H), 5.15 (s, 2H), 4.17 (t, *J* = 6.4 Hz, 2H), 2.75–2.65 (m, 2H), 2.64–2.54 (m, 4H), 2.10 (m, 2H), 1.92–1.71 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.50, 157.62, 153.04, 143.93, 139.24, 132.86, 131.93, 128.90, 128.87, 124.69, 123.49, 123.18, 121.37, 106.86, 66.96, 54.26, 53.11, 49.80, 28.62, 23.48 ppm. Elem. Anal. ($C_{22}H_{23}N_3O_2 \times 0.7 \cdot CH_2Cl_2$) calcd: C, 64.78; H, 5.84; Cl, 11.79; N, 9.98; O, 7.60 found: C, 64.81; H, 5.88; N, 10.15.

7.3.26. 8-(3-(Diethylamino)propoxy)isoindolo[1,2-*b*]quinazolin-10(12*H*)-one (18)

Starting from 8-(3-bromopropoxy)isoindolo[1,2-*b*]quinazolin-10(12*H*)-one **12** (230 mg, 0.62 mmol) and diethylamine (68 mg, 0.93 mmol). The title compound was obtained as a beige solid (100 mg, 44%). Mp = 120–123 °C. R_t: 1.508 min, HRESIMS ($C_{22}H_{25}N_3O_2$+H)$^+$, *m*/*z* calcd: 364.202; found: 364.2021. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.13 (dd, *J* = 10.2, 4.6 Hz, 1H), 7.79–7.70 (m, 2H), 7.65–7.50 (m, 3H), 7.43–7.32 (m, 1H), 5.15 (s, 2H), 4.15 (t, *J* = 6.2 Hz, 2H), 2.72–2.64 (m, 2H), 2.59 (q, *J* = 7.2 Hz, 4H), 2.11–1.89 (m, 2H), 1.06 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.51, 157.66, 153.02, 143.91, 139.24, 132.87, 131.93, 128.89, 128.87, 124.66, 123.49, 123.18, 121.38, 106.88, 66.91, 49.79, 49.34, 46.98, 26.75, 11.62 ppm. Elem. Anal. ($C_{22}H_{25}N_3O_2 \times 0.2 \cdot CH_2Cl_2$) calcd: C, 70.09; H, 6.73; Cl, 3.73; N, 11.05; O, 8.41 found: C, 70.02; H, 6.73; N, 10.82.

7.3.27. 8-(3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)propoxy)isoindolo[1,2-*b*]quinazolin-10(12*H*)-one (19)

Starting from 8-(3-bromopropoxy)isoindolo[1,2-*b*]quinazolin-10(12*H*)-one **12** (230 mg, 0.62 mmol) and 1,2,3,4-tetrahydroisoquinoline (124 mg, 0.93 mmol). The title compound was obtained as beige solid (155 mg, 59%). Mp = 158–160 °C. ESI-MS: 424.0 *m*/*z* [MH]$^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.15 (d, *J* = 6.9 Hz, 1H), 7.82–7.70 (m, 2H), 7.67–7.51 (m, 3H), 7.40 (dd, *J* = 9.0, 2.9 Hz, 1H), 7.11 (d, *J* = 3.8 Hz, 5H), 5.14 (s, 2H), 4.19 (m, 2H), 3.65 (t, *J* = 13.4 Hz, 4H), 2.94 (dd, *J* = 14.6, 10.6 Hz, 4H), 2.16 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 160.47, 157.67, 153.04, 143.95, 139.27, 134.32, 134.24, 132.91, 131.92, 128.93, 128.86, 128.66, 126.63, 126.17, 125.64, 124.64, 123.49, 123.19, 121.42, 106.99, 66.93, 56.24, 54.92, 50.96, 49.79, 28.99, 27.06 ppm. Elem. Anal. ($C_{27}H_{25}N_3O_2 \times 0.1 \cdot CH_2Cl_2$) calcd: C, 75.34; H, 5.88; Cl, 1.64; N, 9.73; O, 7.41 found: C, 75.42; H, 5.89; N, 9.78.

7.3.28. 8-(3-(1*H*-Imidazol-1-yl)propoxy)isoindolo[1,2-*b*]quinazolin-10(12*H*)-one (20)

Starting from 8-(3-bromopropoxy)isoindolo[1,2-*b*]quinazolin-10(12*H*)-one **12** (230 mg, 0.62 mmol) and imidazole (63 mg,

0.93 mmol). The title compound was obtained as a beige solid (110 mg, 50%). Mp = 223–226 °C. R_t: 1.443 min, HRESIMS ($C_{21}H_{18}N_4O_2$+H)$^+$, *m*/*z* calcd: 359.1503; found: 359.1504. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.20–8.12 (m, 1H), 7.78 (d, *J* = 9.0 Hz, 1H), 7.71 (d, *J* = 2.9 Hz, 1H), 7.67–7.53 (m, 4H), 7.39 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.08 (s, 1H), 6.95 (s, 1H), 5.16 (s, 2H), 4.23 (t, *J* = 6.9 Hz, 2H), 4.08 (t, *J* = 5.7 Hz, 2H), 2.40–2.22 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.41, 156.94, 153.24, 144.33, 139.27, 137.26, 132.78, 132.08, 130.34, 129.49, 129.18, 128.93, 124.39, 123.53, 123.26, 121.42, 119.01, 106.98, 64.47, 49.83, 43.62, 30.70 ppm. Elem. Anal. ($C_{21}H_{18}N_4O_2 \times 0.4{\cdot}CH_2Cl_2$) calcd: C, 65.51; H, 4.83; Cl, 7.23; N, 14.28; O, 8.16 found: C, 65.42; H, 5.04; N, 14.40.

7.3.29. 10-(3-(Piperidin-1-yl)propoxy)-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (21)

Starting from 10-(3-bromopropoxy)-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one **13** (240 mg, 0.62 mmol) and piperidine (80 mg, 0.93 mmol). The title compound was obtained as beige solid (145 mg, 60%). Mp = 127–129 °C. R_t: 1.814 min, HRESIMS ($C_{24}H_{27}N_3O_2$+H)$^+$, *m*/*z* calcd: 390.2176; found: 390.2188. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.43 (m, 1H), 7.67 (m, 2H), 7.49–7.37 (m, 2H), 7.34 (d, *J* = 2.9 Hz, 1H), 7.27 (dd, *J* = 6.3, 2.2 Hz, 1H), 4.50–4.34 (m, 2H), 4.13 (m, 2H), 3.09 (m, 2H), 2.50 (m, 6H), 2.14–1.95 (m, 2H), 1.61 (m, 4H), 1.53–1.32 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.52, 157.75, 147.31, 142.36, 136.70, 131.31, 129.74, 129.19, 127.66, 127.61, 127.49, 124.92, 121.46, 106.92, 67.12, 55.96, 54.65, 39.74, 27.53, 26.69, 25.90, 24.40 ppm. Elem. Anal. ($C_{24}H_{27}N_3O_2 \times 0.28{\cdot}CH_2Cl_2$) calcd: 70.56; H, 6.72; Cl, 4.80; N, 10.17; O, 7.74 found: C, 70.75; H, 6.66; N, 9.97.

7.3.30. 10-(3-(Azepan-1-yl)propoxy)-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (22)

Starting from 10-(3-bromopropoxy)-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one **13** (240 mg, 0.62 mmol) and azepane (92 mg, 0.93 mmol). The title compound was obtained as beige solid (164 mg, 66%). Mp = 101–103 °C. R_t: 1.922 min, HRESIMS ($C_{25}H_{29}N_3O_2$+H)$^+$, *m*/*z* calcd: 404.2333; found: 404.2338. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.48–8.38 (m, 1H), 7.68 (dd, *J* = 9.0, 5.9 Hz, 2H), 7.49–7.37 (m, 2H), 7.34 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.30–7.25 (m, 1H), 4.51–4.34 (m, 2H), 4.14 (t, *J* = 6.3 Hz, 2H), 3.09 (t, *J* = 6.4 Hz, 2H), 2.80–2.63 (m, 6H), 2.14–1.94 (m, 2H), 1.76–1.52 (m, 8H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.53, 157.76, 147.32, 142.37, 136.70, 131.32, 129.74, 129.21, 127.67, 127.62, 127.49, 124.89, 121.48, 106.97, 66.94, 55.50, 54.72, 39.75, 27.75, 27.54, 27.23, 27.02 ppm. Elem. Anal. ($C_{25}H_{29}N_3O_2 \times 0.15{\cdot}CH_2Cl_2$) calcd: C, 72.57; H, 7.09; Cl, 2.56; N, 10.09; O, 7.69 found: C, 72.62; H, 7.01; N, 9.87.

7.3.31. 10-(3-(Pyrrolidin-1-yl)propoxy)-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (23)

Starting from 10-(3-bromopropoxy)-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one **13** (240 mg, 0.62 mmol) and pyrrolidine (66 mg, 0.93 mmol). The title compound was obtained as a beige solid (150 mg, 64%). Mp = 124–125 °C. R_t: 1.730 min, HRESIMS ($C_{23}H_{25}N_3O_2$+H)$^+$, *m*/*z* calcd: 376.202; found: 376.2017. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.43 (m, 3H), 7.67 (dd, *J* = 9.3, 5.9 Hz, 6H), 7.49–7.37 (m, 6H), 7.34 (dd, *J* = 8.9, 3.0 Hz, 3H), 7.30–7.25 (m, 4H), 4.50–4.34 (m, 6H), 4.16 (t, *J* = 6.3 Hz, 6H), 3.12 (dt, *J* = 12.9, 6.2 Hz, 8H), 2.85–2.72 (m, 8H), 2.66 (d, *J* = 5.5 Hz, 12H), 2.20–2.06 (m, 6H), 1.92–1.79 (m, 12H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.50, 157.60, 147.38, 142.44, 136.71, 131.34, 129.72, 129.24, 127.67, 127.62, 127.50, 124.82, 121.47, 107.03, 66.75, 54.22, 53.12, 39.75, 28.29, 27.53, 23.48 ppm. Elem. Anal. ($C_{23}H_{25}N_3O_2 \times 0.3{\cdot}CH_2Cl_2$) calcd: C, 69.80; H, 6.44; Cl, 5.31; N, 10.48; O, 7.98 found: C, 69.72; H, 6.58; N, 10.56.

7.3.32. 10-(3-(Diethylamino)propoxy)-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (24)

Starting from 10-(3-bromopropoxy)-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one **13** (240 mg, 0.62 mmol) and diethylamine (68 mg, 0.93 mmol). The title compound was obtained as a beige solid (130 mg, 56%). Mp = 153–155 °C. R_t: 1.771 min, HRESIMS ($C_{23}H_{27}N_3O_2$+H)$^+$, *m*/*z* calcd: 378.2176; found: 378.2172. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.48–8.38 (m, 1H), 7.66 (dd, *J* = 8.6, 5.9 Hz, 2H), 7.47–7.37 (m, 2H), 7.33 (dt, *J* = 5.5, 2.8 Hz, 1H), 7.29–7.23 (m, 1H), 4.52–4.28 (m, 2H), 4.16 (m, 2H), 3.06 (m, 2H), 2.69 (dd, *J* = 8.2, 6.7 Hz, 2H), 2.61 (q, *J* = 7.2 Hz, 4H), 2.11–1.93 (m, 2H), 1.07 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.50, 157.68, 147.32, 142.38, 136.69, 131.31, 129.72, 129.20, 127.65, 127.60, 127.48, 124.81, 121.47, 107.00, 66.80, 49.31, 46.96, 39.74, 27.52, 26.57, 11.48 ppm. Elem. Anal. ($C_{23}H_{27}N_3O_2 \times 0.25{\cdot}CH_2Cl_2$) calcd: C, 70.04; H, 6.95; Cl, 4.45; N, 10.54; O, 8.03 found: C, 70.09; H, 6.90; N, 10.49.

7.3.33. 10-(3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)propoxy)-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (25)

Starting from 10-(3-bromopropoxy)-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one **13** (240 mg, 0.62 mmol) and 1,2,3,4-tetrahydroisoquinoline (124 mg, 0.93 mmol). The title compound was obtained as a beige solid (170 mg, 63%). Mp = 109–111 °C. R_t: 2.009 min, HRESIMS ($C_{28}H_{27}N_3O_2$+H)$^+$, *m*/*z* calcd: 438.2176; found: 438.2172. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.48–8.39 (m, 1H), 7.75–7.64 (m, 2H), 7.48–7.40 (m, 2H), 7.40–7.31 (m, 2H), 7.31–7.24 (m, 2H), 7.11 (dd, *J* = 4.6, 3.3 Hz, 2H), 4.48–4.34 (m, 2H), 4.20 (t, *J* = 6.3 Hz, 2H), 3.69 (s, 2H), 3.09 (t, *J* = 6.4 Hz, 2H), 2.93 (t, *J* = 5.8 Hz, 2H), 2.79–2.70 (m, 4H), 2.22–2.09 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.50, 160.50, 157.72, 147.34, 142.40, 136.71, 134.25, 131.32, 129.22, 128.68, 127.67, 127.61, 127.50, 127.11, 126.62, 126.19, 125.65, 124.85, 121.49, 107.05, 66.87, 56.18, 54.91, 51.02, 39.75, 29.06, 27.53, 26.99 ppm. Elem. Anal. ($C_{28}H_{27}N_3O_2 \times 0.15{\cdot}CH_2Cl_2$) calcd: C, 75.09; H, 6.11; Cl, 2.36; N, 9.33; O, 7.11 found: C, 74.93; H, 6.11; N, 9.22.

7.3.34. 10-(3-(1*H*-Imidazol-1-yl)propoxy)-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (26)

Starting from 10-(3-bromopropoxy)-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one **13** (240 mg, 0.62 mmol) and imidazole (63 mg, 0.93 mmol). The title compound was obtained as beige solid (110 mg, 48%). Mp = 164–166 °C. R_t: 1.693 min, HRESIMS ($C_{22}H_{20}N_4O_2$+H)$^+$, *m*/*z* calcd: 373.1659; found: 373.1658. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.50–8.37 (m, 1H), 7.76–7.69 (m, 1H), 7.62 (d, *J* = 2.9 Hz, 1H), 7.50 (s, 1H), 7.49–7.38 (m, 2H), 7.35 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.31–7.24 (m, 1H), 7.06 (t, *J* = 0.9 Hz, 1H), 6.94 (t, *J* = 1.2 Hz, 1H), 4.45–4.36 (m, 2H), 4.21 (t, *J* = 6.9 Hz, 2H), 4.05 (t, *J* = 5.7 Hz, 2H), 3.09 (t, *J* = 6.4 Hz, 2H), 2.40–2.20 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.44, 157.03, 147.65, 142.76, 137.27, 136.74, 135.12, 131.46, 129.63, 129.47, 127.71, 127.65, 127.53, 124.58, 121.49, 119.00, 107.07, 64.44, 43.56, 39.79, 30.69, 27.49 ppm. Elem. Anal. ($C_{22}H_{20}N_4O_2 \times 0.125{\cdot}CHCl_3$) calcd: C, 68.61; H, 5.24; Cl, 3.43; N, 14.46; O, 8.26 found: C, 68.24; H, 5.42; N, 14.85.

7.3.35. 11-(3-(Piperidin-1-yl)propoxy)-6,7-dihydrobenzo[3,4]azepino[2,1-*b*]quinazolin-9(5*H*)-one (27)

Starting from 11-(3-bromopropoxy)-6,7-dihydrobenzo[3,4]azepino[2,1-*b*]quinazolin-9(5*H*)-one **14** (250 mg, 0.62 mmol) and piperidine (80 mg, 0.93 mmol). The title compound was obtained as a yellow oil (153 mg, 61%). R_t: 1.734 min, HRESIMS ($C_{25}H_{29}N_3O_2$+H)$^+$, *m*/*z* calcd: 404.2333; found: 404.2336. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.91–7.76 (m, 1H), 7.76–7.60 (m, 2H), 7.50–7.37 (m, 2H), 7.34 (dd, *J* = 8.8, 3.0 Hz, 1H), 7.26–7.20 (m, 1H), 5.15–3.85 (m, 3H), 2.81–2.65 (m, 2H), 2.52–2.33 (m, 6H), 2.31–1.92 (m, 4H), 1.60 (m, 4H), 1.50–1.34 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.49,

157.89, 154.14, 142.39, 137.89, 135.04, 131.03, 129.20, 128.90, 128.57, 127.44, 124.89, 121.18, 106.88, 67.14, 55.93, 54.66, 41.54, 29.78, 28.77, 26.70, 25.93, 24.41 ppm. Elem. Anal. ($C_{25}H_{29}N_3O_2 \times 0.6{\cdot}CH_2Cl_2$) calcd: C, 67.65; H, 6.70; Cl, 9.36; N, 9.25; O, 7.04 found: C, 67.62; H, 6.73; N, 9.39.

7.3.36. 11-(3-(Azepan-1-yl)propoxy)-6,7-dihydrobenzo[3,4]azepino[2,1-*b*]quinazolin-9(5*H*)-one (28)

Starting from 11-(3-bromopropoxy)-6,7-dihydrobenzo[3,4]azepino[2,1-*b*]quinazolin-9(5*H*)-one **14** (250 mg, 0.62 mmol) and azepane (92 mg, 0.93 mmol). The title compound was obtained as a yellow oil (170 mg, 66%). R_t: 1.833 min, HRESIMS ($C_{26}H_{31}N_3O_2$+H)$^+$, *m*/*z* calcd: 418.2489; found: 418.2495. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88–7.76 (m, 1H), 7.68 (t, *J* = 5.5 Hz, 2H), 7.51–7.38 (m, 2H), 7.35 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.24 (dd, *J* = 6.9, 1.7 Hz, 1H), 4.98–3.96 (m, 4H), 2.75 (dd, *J* = 6.7, 2.7 Hz, 7H), 2.22 (s, 2H), 2.14–2.01 (m, 2H), 1.79–1.54 (m, 10H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.49, 157.80, 154.20, 142.44, 137.90, 135.02, 131.05, 129.24, 128.90, 128.59, 127.45, 124.80, 121.19, 106.96, 66.82, 55.44, 55.21, 54.74, 41.55, 29.78, 28.77, 27.40, 27.00 ppm. Elem. Anal. ($C_{26}H_{31}N_3O_2 \times 0.6{\cdot}CH_2Cl_2$) calcd: C, 68.19; H, 6.93; Cl, 9.08; N, 8.97; O, 6.83 found: C, 67.93; H, 7.11; N, 9.17.

7.3.37. 11-(3-(Pyrrolidin-1-yl)propoxy)-6,7-dihydrobenzo[3,4]azepino[2,1-*b*]quinazolin-9(5*H*)-one (29)

Starting from 11-(3-bromopropoxy)-6,7-dihydrobenzo[3,4]azepino[2,1-*b*]quinazolin-9(5*H*)-one **14** (250 mg, 0.62 mmol) and pyrrolidine (66 mg, 0.93 mmol). The title compound was obtained as a brown oil (110 mg, 46%). R_t: 1.677 min, HRESIMS ($C_{24}H_{27}N_3O_2$+H)$^+$, *m*/*z* calcd: 390.2176; found: 390.2174. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.89–7.80 (m, 1H), 7.69 (t, *J* = 6.0 Hz, 2H), 7.50–7.39 (m, 2H), 7.35 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.24 (dd, *J* = 3.9, 2.8 Hz, 1H), 4.18 (t, *J* = 6.2 Hz, 4H), 2.96–2.65 (m, 8H), 2.21 (dd, *J* = 14.3, 6.6 Hz, 4H), 1.91 (s, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.47, 157.60, 154.63, 142.48, 137.90, 135.01, 131.07, 129.30, 128.91, 128.60, 127.46, 124.70, 121.18, 107.03, 66.54, 54.16, 53.12, 41.57, 29.78, 28.77, 27.89, 23.49 ppm. Elem. Anal. ($C_{24}H_{27}N_3O_2 \times 0.85{\cdot}CH_2Cl_2$) calcd: C, 64.65; H, 6.27; Cl, 13.05; N, 9.10; O, 6.93 found: C, 64.61; H, 6.22; N, 9.00.

7.3.38. 11-(3-(Diethylamino)propoxy)-6,7-dihydrobenzo[3,4]azepino[2,1-*b*]quinazolin-9(5*H*)-one (30)

Starting from 11-(3-bromopropoxy)-6,7-dihydrobenzo[3,4]azepino[2,1-*b*]quinazolin-9(5*H*)-one **14** (250 mg, 0.62 mmol) and diethylamine (68 mg, 0.93 mmol). The title compound was obtained as dark yellow oil (130 mg, 56%). R_t: 1.708 min, HRESIMS ($C_{24}H_{29}N_3O_2$+H)$^+$, *m*/*z* calcd: 392.2333; found: 392.2329. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.90–7.78 (m, 1H), 7.69 (t, *J* = 6.0 Hz, 2H), 7.50–7.39 (m, 2H), 7.35 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.24 (dd, *J* = 3.8, 2.8 Hz, 1H), 4.78–3.77 (m, 4H), 2.91–2.59 (m, 8H), 2.38–1.98 (m, 4H), 1.24–1.04 (m, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.48, 157.65, 154.28, 142.52, 137.90, 135.02, 131.07, 129.30, 128.91, 128.60, 127.46, 124.70, 121.22, 107.02, 66.54, 49.26, 46.94, 41.57, 29.78, 28.77, 26.08, 10.98 ppm. Elem. Anal. ($C_{24}H_{29}N_3O_2 \times 0.1{\cdot}CH_2Cl_2$) calcd: C, 72.36; H, 7.36; Cl, 1.77; N, 10.51; O, 8.00 found: C, 72.18; H, 7.33; N, 10.18.

7.3.39. 11-(3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)propoxy)-6,7-dihydrobenzo[3,4]azepino[2,1-*b*]quinazolin-9(5*H*)-one (31)

Starting from 11-(3-bromopropoxy)-6,7-dihydrobenzo[3,4]azepino[2,1-*b*]quinazolin-9(5*H*)-one **14** (250 mg, 0.62 mmol) and 1,2,3,4-tetrahydroisoquinoline (124 mg, 0.93 mmol). The title compound was obtained as a yellow oil (170 mg, 63%). R_t: 1.951 min, HRESIMS ($C_{29}H_{29}N_3O_2$+H)$^+$, *m*/*z* calcd: 452.2333; found: 452.2328. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.84 (dd, *J* = 8.7, 4.0 Hz, 1H), 7.68 (dd, *J* = 8.8, 5.0 Hz, 2H), 7.44 (pd, *J* = 7.5, 3.8 Hz, 2H), 7.30–7.21 (m, 2H), 7.16–7.07 (m, 4H), 4.91–3.90 (m, 4H), 3.68 (d, *J* = 13.5 Hz, 2H), 2.94 (t, *J* = 5.7 Hz, 2H), 2.74 (m, 6H), 2.15 (qd, *J* = 14.3, 6.2 Hz, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.47, 157.83, 154.20, 142.44, 137.91, 135.05, 134.41, 134.17, 131.04, 129.25, 128.92, 128.68, 128.59, 127.45, 126.62, 126.23, 125.69, 124.81, 121.21, 107.01, 66.85, 56.10, 54.84, 50.98, 41.55, 29.78, 28.97, 28.77, 26.92 ppm. Elem. Anal. ($C_{29}H_{29}N_3O_2 \times 0.5{\cdot}CH_2Cl_2$) calcd: C, 71.72; H, 6.12; Cl, 7.18; N, 8.51; O, 6.48 found: C, 71.46; H, 6.08; N, 8.47.

7.3.40. 11-(3-(1*H*-Imidazol-1-yl)propoxy)-6,7-dihydrobenzo[3,4]azepino[2,1-*b*]quinazolin-9(5*H*)-one (32)

Starting from 11-(3-bromopropoxy)-6,7-dihydrobenzo[3,4]azepino[2,1-*b*]quinazolin-9(5*H*)-one **14** (250 mg, 0.62 mmol) and imidazole (63 mg, 0.93 mmol). The title compound was obtained as a yellow semi-solid. (110 mg, 48%). R_t: 1.636 min, HRESIMS ($C_{23}H_{22}N_4O_2$+H)$^+$, *m*/*z* calcd: 387.1816; found: 387.1812. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.90–7.78 (m, 1H), 7.78–7.58 (m, 3H), 7.50–7.39 (m, 2H), 7.36 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.11 (s, 1H), 6.95 (dd, *J* = 5.9, 3.4 Hz, 1H), 5.40–4.48 (m, 2H), 4.27 (t, *J* = 6.8 Hz, 2H), 4.08 (t, *J* = 5.6 Hz, 2H), 2.75 (t, *J* = 6.9 Hz, 2H), 2.46–2.10 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.40, 157.10, 154.54, 142.81, 137.90, 137.07, 134.95, 131.14, 129.52, 128.92, 128.62, 128.50, 127.48, 124.51, 121.24, 119.19, 107.06, 64.42, 43.93, 41.61, 30.59, 29.77, 28.77 ppm. Elem. Anal. ($C_{23}H_{22}N_4O_2 \times 0.2{\cdot}CH_2Cl_2$) calcd: C, 69.07; H, 5.60; Cl, 3.52; N, 13.89; O, 7.93 found: C, 69.16; H, 5.68; N, 14.20.

7.3.41. 7-(3-(Piperidin-1-yl)propoxy)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (42)

Starting from 7-(3-bromopropoxy)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one **39** (200 mg, 0.62 mmol) and piperidine (80 mg, 0.93 mmol). The title compound was obtained as a white solid (120 mg, 59%). Mp = 123–125 °C. R_t: 1.1060 min, HRESIMS ($C_{19}H_{25}N_3O_2$+H)$^+$, *m*/*zm*/*z* calcd: 328.202; found: 328.202. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62 (d, *J* = 3 Hz, 1H), 7.55 (d, *J* = 9.0 Hz, 1H), 7.30 (m, 1H), 4.20 (t, *J* = 7.5 Hz, 2H), 4.11 (t, *J* = 6.3 Hz, 2H), 3.15 (t, *J* = 7.8 Hz, 2H), 2.64–2.48 (m, 6H) 2.22–2.33 (m, 2H), 2.14–2.05 (m, 2H), 1.61–1.73 (m, 4H), 1.42–1.52 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.72, 157.48, 156.57, 144.03, 128.52, 124.02, 121.18, 107.10, 65.66, 55.35, 53.72, 46.53, 32.34, 24.39, 23.09, 22.42, 19.71 ppm. Elem. Anal. ($C_{19}H_{25}N_3O_2 \times 1.33{\cdot}CHCl_3$) calcd: C, 50.22; H, 5.46; Cl, 29.09; N, 8.64; O, 6.58 found: C, 49.90; H, 5.82; N, 8.93 ppm.

7.3.42. 7-(3-(Azepan-1-yl)propoxy)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (43)

Starting from 7-(3-bromopropoxy)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one **39** (200 mg, 0.62 mmol) and azepane (92 mg, 0.93 mmol). The title compound was obtained as yellow viscous oil (164 mg, 77%). R_t: 1.210 min, HRESIMS ($C_{20}H_{27}N_3O_2$+H)$^+$, *m*/*z* calcd: 342.2182; found: 342.2176. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.61 (d, *J* = 2.9 Hz, 1H), 7.54 (d, *J* = 8.9 Hz, 1H), 7.33–7.25 (m, 1H), 4.23–4.14 (m, 2H), 4.10 (t, *J* = 6.3 Hz, 2H), 3.21–3.05 (m, 2H), 2.76–2.61 (m, 6H), 2.36–2.19 (m, 2H), 2.07–1.92 (m, 2H), 1.61 (m, 8H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.85, 157.43, 157.11, 143.59, 128.20, 124.54, 121.18, 106.70, 66.91, 55.49, 54.68, 46.49, 36.49, 32.24, 31.42, 27.78, 27.24, 26.99, 19.68 ppm. Elem. Anal. ($C_{20}H_{27}N_3O_2 \times 0.56{\cdot}CHCl_3$) calcd: C, 60.48; H, 6.80; Cl, 14.59; N, 10.29; O, 7.84 found: C, 60.36; H, 6.95; N, 10.02.

7.3.43. 7-(3-(Pyrrolidin-1-yl)propoxy)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (44)

Starting from 7-(3-bromopropoxy)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one **39** (200 mg, 0.62 mmol) and pyrrolidine (66 mg, 0.93 mmol). The title compound was obtained as a yellow

viscous oil (150 mg, 77%). ESI-MS. R_t: 1.034 min, HRESIMS ($C_{18}H_{23}N_3O_2$+H)$^+$, *m*/*z* calcd: 314.1863; found: 314.1871. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.58 (d, *J* = 2.9 Hz, 1H), 7.50 (t, *J* = 6.8 Hz, 1H), 7.30–7.22 (m, 1H), 4.12 (m, 4H), 3.10 (dd, *J* = 10.4, 5.5 Hz, 2H), 2.76–2.67 (m, 2H), 2.67–2.58 (m, 4H), 2.34–2.17 (m, 2H), 2.17–2.01 (m, 2H), 1.86–1.76 (m, 4H) pm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.79 (NCN), 157.23, 157.19, 143.62, 128.20, 124.45, 121.14, 106.70, 66.69, 54.19, 53.07, 46.49, 32.22, 28.25, 23.44, 19.65 ppm. Elem. Anal. ($C_{18}H_{23}N_3O_2 \times 0.3 \cdot CHCl_3$) calcd: C, 62.94; H, 6.73; Cl, 9.14; N, 12.03; O, 9.16 found: C, 62.69; H, 6.93; N, 12.15.

7.3.44. 7-(3-(Diethylamino)propoxy)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (45)

Starting from 7-(3-bromopropoxy)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one **39** (200 mg, 0.62 mmol) and diethylamine (68 mg, 0.93 mmol). The title compound was obtained as a yellow solid (150 mg, 62%). Mp = 78–80 °C. R_t: 1.067 min, HRESIMS ($C_{18}H_{25}N_3O_2$+H)$^+$, *m*/*z* calcd: 316.202; found: 316.2023. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62 (d, *J* = 2.9 Hz, 1H), 7.54 (d, *J* = 8.9 Hz, 1H), 7.30 (dd, *J* = 8.9, 2.9 Hz, 1H), 4.22–4.14 (m, 2H), 4.10 (t, *J* = 6.3 Hz, 2H), 3.13 (dd, *J* = 10.3, 5.5 Hz, 2H), 2.67–2.60 (m, 2H), 2.55 (q, *J* = 7.1 Hz, 4H), 2.35–2.16 (m, 2H), 2.06–1.83 (m, 2H), 1.02 (t, *J* = 7.1 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.86, 157.44, 157.10, 143.58, 128.20, 124.54, 121.18, 106.70, 66.87, 49.31, 46.97, 46.49, 32.24, 26.78, 19.68, 11.67 ppm. Elem. Anal. ($C_{18}H_{25}N_3O_2 \times 0.46$ ethylacetate) calcd: C, 66.95; H, 8.12; N, 11.81; O, 13.13 found: C, 66.57; H, 7.86; N, 12.26.

7.3.45. 7-(3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)propoxy)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (46)

Starting from 7-(3-bromopropoxy)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one **39** (200 mg, 0.62 mmol) and 1,2,3,4-tetrahydroisoquinoline (124 mg, 0.93 mmol). The title compound was obtained as a pale yellow solid (165 mg, 71%). Mp = 140–142 °C. R_t: 1.357 min, HRESIMS ($C_{23}H_{25}N_3O_2$+H)$^+$, *m*/*z* calcd: 376.202; found: 376.2023. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.63 (d, *J* = 2.9 Hz, 1H), 7.56 (d, *J* = 8.9 Hz, 1H), 7.32 (dd, *J* = 8.9, 2.9 Hz, 1H), 7.17–6.94 (m, 5H), 4.26–4.10 (m, 2H), 3.66 (d, *J* = 4.0 Hz, 2H), 3.13 (dd, *J* = 10.4, 5.5 Hz, 2H), 2.98–2.85 (m, 2H), 2.73 (m 4H), 2.34–2.01 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.83, 157.41, 157.14, 143.63, 134.71, 134.30, 128.66, 128.23, 126.59, 126.13, 125.61, 124.53, 121.21, 106.76, 66.85, 56.23, 54.92, 51.04, 46.49, 32.25, 29.13, 27.02, 19.67 ppm. Elem. Anal. ($C_{23}H_{25}N_3O_2 \times 0.56$ ethylacetate) calcd: C, 71.36; H, 6.99; N, 9.89; O, 11.75 found: C, 71.12; H, 6.60; N, 9.97.

7.3.46. 7-(3-(1*H*-Imidazol-1-yl)propoxy)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (47)

Starting from 7-(3-bromopropoxy)-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one **39** (200 mg, 0.62 mmol) and imidazole (65 mg, 0.93 mmol). The title compound was obtained as beige solid (145 mg, 75%). Mp = 158–160 °C. R_t: 1.137 min, HRESIMS ($C_{17}H_{18}N_4O_2$+H)$^+$, *m*/*z* calcd: 311.1503; found: 311.1508. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.63–7.54 (m, 2H), 7.50 (s, 1H), 7.31 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.06 (s, 1H), 6.92 (s, 1H), 4.20 (m, 4H), 4.10–3.92 (m, 2H), 3.17 (dd, *J* = 18.3, 10.5 Hz, 2H), 2.28 (qd, *J* = 7.9, 2.5 Hz, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.75, 157.49, 156.74, 144.01, 137.28, 129.65, 128.52, 124.25, 121.26, 118.93, 106.82, 64.41, 46.53, 43.53, 32.28, 30.69, 19.67 ppm. Elem. Anal. ($C_{17}H_{18}N_4O_2 \times 0.4$ ethylacetate) calcd: C, 64.64; H, 6.18; N, 16.21; O, 12.96 found: C, 64.95; H, 5.96; N, 16.05.

7.3.47. 2-(3-(Piperidin-1-yl)propoxy)-8,9-dihydro-6*H*-pyrido[2,1-*b*]quinazolin-11(7*H*)-one (48)

Starting from 2-(3-bromopropoxy)-8,9-dihydro-6*H*-pyrido[2,1-*b*]quinazolin-11(7*H*)-one **40** (210 mg, 0.62 mmol) and piperidine (80 mg, 0.93 mmol). The title compound was obtained as beige solid (135 mg, 64%). Mp = 120–122 °C. R_t: 1.098 min, HRESIMS ($C_{20}H_{27}N_3O_2$+H)$^+$, *m*/*z* calcd: 342.2176; found: 342.2178. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.59 (t, *J* = 3.8 Hz, 1H), 7.50 (d, *J* = 8.9 Hz, 1H), 7.33–7.23 (m, 1H), 4.08 (m, 4H), 2.96 (t, *J* = 6.6 Hz, 2H), 2.55–2.33 (m, 6H), 2.07–1.87 (m, 6H), 1.59 (m, 4H), 1.50–1.35 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.07, 157.28, 152.42, 141.98, 127.93, 124.93, 121.03, 106.55, 67.06, 55.95, 54.64, 42.44, 31.77, 26.69, 25.91, 24.40, 22.18, 19.42 ppm. Elem. Anal. ($C_{20}H_{27}N_3O_2 \times 0.25 \cdot CH_2Cl_2$) calcd: C, 67.06; H, 7.64; Cl, 4.89; N, 11.59; O, 8.82 found: C, 67.15; H, 7.65; N, 11.60.

7.3.48. 2-(3-(Azepan-1-yl)propoxy)-8,9-dihydro-6*H*-pyrido[2,1-*b*]quinazolin-11(7*H*)-one (49)

Starting from 2-(3-bromopropoxy)-8,9-dihydro-6*H*-pyrido[2,1-*b*]quinazolin-11(7*H*)-one **40** (210 mg, 0.62 mmol) and azepane (92 mg, 0.93 mmol). The title compound was obtained as beige solid (145 mg, 66%). Mp = 117–120 °C. R_t: 1.212 min, HRESIMS ($C_{21}H_{29}N_3O_2$+H)$^+$, *m*/*z* calcd: 356.2333; found: 356.2333. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.56 (d, *J* = 2.9 Hz, 1H), 7.47 (t, *J* = 5.8 Hz, 1H), 7.27 (dd, *J* = 8.9, 2.9 Hz, 1H), 4.17–3.96 (m, 4H), 2.92 (q, *J* = 6.5 Hz, 2H), 2.75–2.30 (m, 6H), 2.04–1.82 (m, 6H), 1.74–1.48 (m, 8H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.03, 157.29, 152.40, 141.94, 127.90, 124.88, 121.02, 106.56, 66.89, 55.48, 54.66, 42.42, 31.74, 27.84, 27.28, 26.98, 22.17, 19.40 ppm. Elem. Anal. ($C_{21}H_{29}N_3O_2 \times 0.35 \cdot CH_2Cl_2$) calcd: C, 66.57; H, 7.77; Cl, 6.44; N, 10.91; O, 8.31 found: C, 66.55; H, 7.67; N, 10.97.

7.3.49. 2-(3-(Pyrrolidin-1-yl)propoxy)-8,9-dihydro-6*H*-pyrido[2,1-*b*]quinazolin-11(7*H*)-one (50)

Starting from 72-(3-bromopropoxy)-8,9-dihydro-6*H*-pyrido[2,1-*b*]quinazolin-11(7*H*)-one **40** (210 mg, 0.62 mmol) and pyrrolidine (66 mg, 0.93 mmol). The title compound was obtained as beige solid (140 mg, 69%). Mp = 121–123 °C. ESI-MS. R_t: 1.021 min, HRESIMS ($C_{19}H_{25}N_3O_2$+H)$^+$, *m*/*z* calcd: 328.202; found: 328.202. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.58 (d, *J* = 2.9 Hz, 1H), 7.49 (d, *J* = 8.9 Hz, 1H), 7.33–7.25 (m, 1H), 4.11 (t, *J* = 6.4 Hz, 2H), 4.05 (t, *J* = 6.2 Hz, 2H), 2.95 (t, *J* = 6.6 Hz, 2H), 2.69–2.59 (m, 2H), 2.58–2.46 (m, 4H), 2.10–1.86 (m, 6H), 1.83–1.71 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.04, 157.25, 152.41, 141.98, 127.92, 124.90, 121.03, 106.58, 66.93, 54.25, 53.09, 42.42, 31.76, 28.70, 23.45, 22.18, 19.41 ppm. Elem. Anal. ($C_{19}H_{25}N_3O_2 \times 0.15 \cdot CH_2Cl_2$) calcd: C, 67.62; H, 7.50; Cl, 3.13; N, 12.35; O, 9.41 found: C, 67.62; H, 7.37; N, 12.34.

7.3.50. 2-(3-(Diethylamino)propoxy)-8,9-dihydro-6*H*-pyrido[2,1-*b*]quinazolin-11(7*H*)-one (51)

Starting from 2-(3-bromopropoxy)-8,9-dihydro-6*H*-pyrido[2,1-*b*]quinazolin-11(7*H*)-one **40** (210 mg, 0.62 mmol) and diethylamine (68 mg, 0.93 mmol). The title compound was obtained as beige solid (133 mg, 65%). Mp = 113–115 °C. R_t: 1.074 min, HRESIMS ($C_{19}H_{27}N_3O_2$+H)$^+$, *m*/*z* calcd: 330.2176; found: 330.2178. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.58 (d, *J* = 2.9 Hz, 1H), 7.49 (d, *J* = 8.9 Hz, 1H), 7.28 (dd, *J* = 8.9, 2.9 Hz, 1H), 4.07 (dt, *J* = 10.4, 6.3 Hz, 4H), 2.94 (t, *J* = 6.6 Hz, 2H), 2.56 (m, 6H), 2.05–1.83 (m, 6H), 1.00 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.05, 157.32, 152.37, 141.95, 127.91, 124.87, 121.04, 106.58, 66.90, 49.33, 46.98, 42.41, 31.75, 26.91, 22.18, 19.42, 11.80. Elem. Anal. ($C_{19}H_{27}N_3O_2 \times 0.15 \cdot CH_2Cl_2$) calcd: C, 67.22; H, 8.04; Cl, 3.11; N, 12.28; O, 9.35 found: C, 67.23; H, 8.04; N, 12.26.

7.3.51. 2-(3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)propoxy)-8,9-dihydro-6*H*-pyrido[2,1*b*] quinazolin-11(7*H*)-one (52)

Starting from 2-(3-bromopropoxy)-8,9-dihydro-6*H*-pyrido[2,1-*b*]quinazolin-11(7*H*)-one **40** (210 mg, 0.62 mmol) and 1,2,3,4-tetrahydroisoquinoline (124 mg, 0.93 mmol). The title compound

was obtained as beige solid (154 mg, 64%). Mp = 167–169 °C. R_t: 1.367 min, HRESIMS ($C_{24}H_{27}N_3O_2$+H)$^+$, *m*/*z* calcd: 390.2176; found: 390.2177. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60 (d, *J* = 2.9 Hz, 1H), 7.52 (d, *J* = 8.9 Hz, 1H), 7.34–7.27 (m, 1H), 7.14–7.05 (m, 3H), 7.00 (dd, *J* = 6.9, 4.3 Hz, 1H), 4.16 (t, *J* = 6.3 Hz, 2H), 4.06 (t, *J* = 6.2 Hz, 2H), 3.67 (s, 2H), 2.94 (m, 4H), 2.85–2.67 (m, 4H), 2.21–2.06 (m, 2H), 2.06–1.84 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.04, 157.24, 152.46, 142.02, 134.61, 134.25, 128.66, 127.96, 126.59, 126.15, 125.62, 124.85, 121.06, 106.67, 66.81, 56.17, 54.90, 51.01, 42.43, 31.77, 29.06, 26.98, 22.18, 19.42 ppm. Elem. Anal. ($C_{24}H_{27}N_3O_2 \times 0.2 \cdot CH_2Cl_2$) calcd: C, 71.51; H, 6.79; Cl, 3.49; N, 10.34; O, 7.87 found: C, 71.28; H, 6.62; N, 10.30.

7.3.52. 2-(3-(1*H*-Imidazol-1-yl)propoxy)-8,9-dihydro-6*H*-pyrido[2,1-*b*]quinazolin-11(7*H*)-one (53)

Starting from 2-(3-bromopropoxy)-8,9-dihydro-6*H*-pyrido[2,1-*b*]quinazolin-11(7*H*)-one **40** (210 mg, 0.62 mmol) and imidazole (65 mg, 0.93 mmol). The title compound was obtained as a beige solid (130 mg, 65%). Mp = 105–108 °C. R_t: 1.006 min, HRESIMS ($C_{18}H_{20}N_4O_2$+H)$^+$, *m*/*z* calcd: 325.1659; found: 325.166. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50–7.43 (m, 2H), 7.42 (d, *J* = 5.7 Hz, 1H), 7.23 (dd, *J* = 8.9, 2.9 Hz, 1H), 7.00–6.92 (m, 1H), 6.85 (t, *J* = 1.2 Hz, 1H), 4.12 (t, *J* = 6.9 Hz, 2H), 4.06–3.89 (m, 4H), 2.89 (t, *J* = 6.6 Hz, 2H), 2.28–2.10 (m, 2H), 2.00–1.78 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.85, 156.52, 152.76, 142.27, 137.23, 129.58, 128.14, 124.47, 121.00, 118.90, 106.66, 64.35, 43.45, 42.41, 31.70, 30.62, 22.08, 19.31 ppm. Elem. Anal. ($C_{18}H_{20}N_4O_2$ - $\times 0.31 \cdot CH_2Cl_2$) calcd: C, 62.71; H, 5.93; Cl, 6.27; N, 15.98; O, 9.12 found: C, 62.76; H, 6.02; N, 15.91.

7.3.53. 2-(3-(Piperidin-1-yl)propoxy)-7,8,9,10-tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one (54)

Starting from 2-(3-bromopropoxy)-7,8,9,10-tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one **41** (220 mg, 0.62 mmol) and piperidine (80 mg, 0.93 mmol). The title compound was obtained as pale yellow viscous oil (145 mg, 66%). R_t: 1.307 min, HRESIMS ($C_{21}H_{29}N_3O_2$+H)$^+$, *m*/*z* calcd: 356.2333; found: 356.2338. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.59 (d, *J* = 2.9 Hz, 1H), 7.51 (d, *J* = 8.9 Hz, 1H), 7.29 (dd, *J* = 8.9, 2.9 Hz, 1H), 4.38 (d, *J* = 5.5 Hz, 2H), 4.09 (t, *J* = 6.4 Hz, 2H), 3.07–2.93 (m, 2H), 2.47 (dd, *J* = 20.0, 12.2 Hz, 6H), 2.10–1.95 (m, 2H), 1.83 (s, 6H), 1.59 (m, 4H), 1.51–1.36 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.83, 157.54, 157.34, 141.93, 128.29, 124.77, 120.89, 107.11, 67.08, 55.94, 54.64, 42.98, 37.55, 29.60, 28.17, 26.69, 25.91, 25.55, 24.40 ppm. Elem. Anal. ($C_{21}H_{29}N_3O_2 \times 0.33 \cdot CH_2Cl_2$) calcd: C, 66.80; H, 7.80; Cl, 6.10; N, 10.96; O, 8.34 found: C, 66.80; H, 7.81; N, 10.84.

7.3.54. 2-(3-(Azepan-1-yl)propoxy)-7,8,9,10-tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one (55)

Starting from 2-(3-bromopropoxy)-7,8,9,10-tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one **41** (220 mg, 0.62 mmol) and azepane (92 mg, 0.93 mmol). The title compound was obtained as a yellow thick oil (153 mg, 67%). R_t: 1.420 min, HRESIMS ($C_{22}H_{31}N_3O_2$+H)$^+$, *m*/*z* calcd: 370.2489; found: 370.2493. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.59 (d, *J* = 2.9 Hz, 1H), 7.51 (d, *J* = 8.9 Hz, 1H), 7.29 (dd, *J* = 8.9, 2.9 Hz, 1H), 4.38 (d, *J* = 5.5 Hz, 2H), 4.10 (t, *J* = 6.4 Hz, 2H), 3.09–2.96 (m, 2H), 2.78–2.61 (m, 6H), 2.08–1.93 (m, 2H), 1.83 (s, 6H), 1.71–1.51 (m, 8H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.83, 157.56, 157.33, 141.92, 128.29, 124.73, 120.90, 107.15, 66.92, 55.50, 54.68, 42.97, 37.55, 29.60, 28.17, 27.85, 27.28, 27.00, 25.55 ppm. Elem. Anal. ($C_{22}H_{31}N_3O_2 \times 0.2 \cdot CH_2Cl_2$) calcd: C, 68.99; H, 8.19; Cl, 3.67; N, 10.87; O, 8.28 found: C, 68.89; H, 8.13; N, 10.98.

7.3.55. 2-(3-(Pyrrolidin-1-yl)propoxy)-7,8,9,10-tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one (56)

Starting from 2-(3-bromopropoxy)-7,8,9,10-tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one **41** (220 mg, 0.62 mmol) and pyrrolidine (66 mg, 0.93 mmol). The title compound was obtained as yellow viscous oil (150 mg, 71%). ESI-MS. R_t: 1.239 min, HRESIMS ($C_{20}H_{27}N_3O_2$+H)$^+$, *m*/*z* calcd: 342.2176; found: 342.2181. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.59 (d, *J* = 2.9 Hz, 1H), 7.54–7.47 (m, 1H), 7.28 (dd, *J* = 8.9, 2.9 Hz, 1H), 4.37 (d, *J* = 5.5 Hz, 2H), 4.11 (t, *J* = 6.4 Hz, 2H), 3.08–2.96 (m, 2H), 2.64 (dd, *J* = 9.1, 5.9 Hz, 2H), 2.59–2.48 (m, 4H), 2.12–1.98 (m, 2H), 1.90–1.73 (m, 10H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.81, 157.50, 157.35, 141.93, 128.29, 124.73, 120.89, 107.14, 66.92, 54.24, 53.08, 42.97, 37.55, 29.59, 28.65, 28.17, 25.54, 23.46 ppm. Elem. Anal. ($C_{20}H_{27}N_3O_2$ - $\times 0.2 \cdot CH_2Cl_2$) calcd: C, 67.69; H, 7.71; Cl, 3.96; N, 11.72; O, 8.93 found: C, 67.52; H, 7.69; N, 11.85.

7.3.56. 2-(3-(Diethylamino)propoxy)-7,8,9,10-tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one (57)

Starting from 2-(3-bromopropoxy)-7,8,9,10-tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one **41** (220 mg, 0.62 mmol) and diethylamine (68 mg, 0.93 mmol). The title compound was obtained as yellow viscous oil (142 mg, 67%). R_t: 1.286 min, HRESIMS ($C_{20}H_{29}N_3O_2$+H)$^+$, *m*/*z* calcd: 344.2333; found: 344.2341. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.58 (d, *J* = 2.9 Hz, 1H), 7.50 (d, *J* = 8.9 Hz, 1H), 7.33–7.23 (m, 1H), 4.37 (d, *J* = 5.4 Hz, 2H), 4.09 (t, *J* = 6.3 Hz, 2H), 3.11–2.94 (m, 2H), 2.72–2.42 (m, 6H), 1.93 (m, 2H), 1.81 (s, 6H), 1.01 (t, *J* = 7.1 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.81, 157.55, 157.31, 141.89, 128.26, 124.70, 120.89, 107.12, 66.88, 49.31, 46.97, 42.96, 37.53, 29.58, 28.16, 26.85, 25.54, 11.75 ppm. Elem. Anal. ($C_{20}H_{29}N_3O_2 \times 0.2 \cdot CH_2Cl_2$) calcd: C, 67.31; H, 8.22; Cl, 3.93; N, 11.66; O, 8.88 found: C, 67.45; H, 8.33; N, 11.65.

7.3.57. 2-(3-(3,4-Dihydroisoquinolin-2(1*H*)-yl)propoxy)-7,8,9,10-tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one (58)

Starting from 2-(3-bromopropoxy)-7,8,9,10-tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one **41** (220 mg, 0.62 mmol) and 1,2,3,4-tetrahydroisoquinoline (124 mg, 0.93 mmol). The title compound was obtained as a yellow thick oil (170 mg, 68%). R_t: 1.573 min, HRESIMS ($C_{25}H_{29}N_3O_2$+H)$^+$, *m*/*z* calcd: 404.2333; found: 404.2338. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.61 (t, *J* = 3.2 Hz, 1H), 7.53 (dd, *J* = 8.9, 3.2 Hz, 1H), 7.34–7.27 (m, 1H), 7.17–6.98 (m, 4H), 4.33 (dd, *J* = 25.4, 5.0 Hz, 2H), 4.16 (t, *J* = 6.3 Hz, 2H), 3.67 (s, 2H), 3.08–2.86 (m, 4H), 2.83–2.66 (m, 4H), 2.10 (m, 2H), 1.80 (dd, *J* = 7.6, 4.5 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.80, 157.50, 157.38, 141.96, 134.60, 134.25, 128.66, 128.32, 126.60, 126.16, 125.63, 124.69, 120.92, 107.22, 66.81, 56.17, 54.89, 51.00, 42.97, 37.55, 29.59, 29.06, 28.17, 26.97, 25.55 ppm. Elem. Anal. ($C_{25}H_{29}N_3O_2 \times 0.2 \cdot CH_2Cl_2$) calcd: C, 71.98; H, 7.05; Cl, 3.37; N, 9.99; O, 7.61 found: C, 71.79; H, 6.92; N, 9.97.

7.3.58. 2-(3-(1*H*-Imidazol-1-yl)propoxy)-7,8,9,10-tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one (59)

Starting from 2-(3-bromopropoxy)-7,8,9,10-tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one **41** (220 mg, 0.62 mmol) and imidazole (65 mg, 0.93 mmol). The title compound was obtained as beige solid (138 mg, 66%). Mp = 117–120 °C. R_t: 1.223 min, HRESIMS ($C_{19}H_{22}N_4O_2$+H)$^+$, *m*/*z* calcd: 339.1816; found: 339.1820. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.58–7.50 (m, 2H), 7.46 (s, 1H), 7.32–7.23 (m, 1H), 7.03 (s, 1H), 6.93–6.84 (m, 1H), 4.46–4.28 (m, 2H), 4.18 (t, *J* = 6.9 Hz, 2H), 4.00 (t, *J* = 5.7 Hz, 2H), 3.10–2.95 (m, 2H), 2.33–2.18 (m, 2H), 1.91–1.72 (m, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.71, 157.71, 156.82, 142.30, 137.29, 129.67, 128.57, 124.39, 120.94, 118.93, 107.25, 64.37, 43.49, 43.01, 37.54, 30.66,

29.56, 28.12, 25.51 ppm. Elem. Anal. ($C_{19}H_{22}N_4O_2 \times 0.2 \cdot CH_2Cl_2$) calcd: C, 64.89; H, 6.35; Cl, 3.99; N, 15.76; O, 9.00 found: C, 64.66; H, 6.41; N, 15.77.

7.3.59. 8-(3-Cyclohexylpropoxy)isoindolo[1,2-*b*]quinazolin-10(12*H*)-one (61)

(3-Chloropropyl)cyclohexane (100 mg, 0.62 mmol), 8-hydroxyisoindolo[1,2-*b*]quinazolin-10(12*H*)-one **9** (100 mg, 0.40 mmol), potassium carbonate (150 mg, 0.75 mmol) and catalytic amount of potassium iodide were refluxed in absolute acetonitrile (50 mL) for 24 h. After cooling, the inorganic salts were filtered off and the filtrate was concentrated under reduced pressure. The remaining residue was taken up in aq solution of NaCl, and extracted with methylene chloride. The combined organic extracts were washed with brine and dried over magnesium sulfate. The organic solvent was removed under reduced pressure. The resulting crude product was subjected to column chromatography to afford the title compound as a white solid (115 mg, 77%). Mp = 144 –146 °C. ESI-MS: 375.0 *m*/*z* $[MH]^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.14 (d, J = 7.0 Hz, 1H), 7.81–7.65 (m, 2H), 7.56 (m 3H), 7.38 (dd, J = 8.9, 4.5 Hz, 1H), 5.14 (s, 2H), 4.06 (t, J = 6.6 Hz, 2H), 1.92–1.60 (m, 7H), 1.44–1.08 (m, 6H), 1.01–0.79 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.49, 157.80, 152.95, 139.23, 139.23, 132.82, 131.92, 128.87, 128.82, 124.80, 123.47, 123.21, 121.33, 106.67, 69.01, 49.80, 37.43, 33.66, 33.34, 26.68, 26.52, 26.38 ppm.

Information about crystallization of compound **26** (CCDC No. 983183) and its crystallographic data can be found in the Supporting information.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2014.06.045.

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