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Synthesis and biological evaluation of a small molecule library of 3rd generation multidrug resistance modulators

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ABSTRACT

The development of new modulators possessing high efficacy, low toxicity and high selectivity is a pivotal approach to overcoming P-glycoprotein (P-gp) mediated multidrug resistance (MDR) in tumour cells. In this study 39 compounds are presented which have been synthesized and pharmacologically investigated in our laboratory. Similarly to the potent 3rd generation MDR modulator tariquidar (XR9576) the compounds contain a tetrahydroisoquinoline–ethyl-phenylamine substructure that, in contrast to XR9576, is connected to a smaller hydrophobic part, thus leading to molecules of lower molecular weight. The connection between the tetrahydroisoquinoline–ethyl-phenylamine substructure and the hydrophobic part was achieved through four different types of linkers: amide, urea, amide-ether and amide-styryl. A number of structural modifications in the hydrophobic part were created. The calcein AM assay served as test system to determine the P-gp transport inhibitory potencies of the compounds. For the amide linker derivatives a structure–activity relationship analysis was performed outlining which structural modifications contributed to the inhibitory potency. The compounds containing a bicyclic hydrophobic part with a particular substituent in a specific orientation were identified as the most potent amide derivatives. Among the urea derivatives the compounds with highest inhibitory potency possessed an *ortho*-nitro substituent. The conformational analysis revealed that this position enables the formation of a hydrogen bond to the urea linker thus stabilizing the conformation. Regarding the amide-styryl derivatives the elongation of the amide linker seemed to be most decisive for the observed increase in activity. The most promising candidate in the whole library possess an amide-ether linker and an *ortho*-nitro substituent in the hydrophobic part. This compound inhibites P-gp slightly less than tariquidar and can serve as a lead structure for new potent P-gp modulators.

1. Introduction

The resistance of tumour cells against cytotoxic drugs is a significant limitation to successful chemotherapeutic treatment of cancer. Often the drug efflux by transport proteins is an underlying mechanism for multidrug resistance (MDR). In MDR tumour cells, various members of the ATP-binding cassette (ABC) family of transport proteins can simultaneously be overexpressed: P-glycoprotein (P-gp, ABCB1), the breast cancer-resistance protein (BCRP, ABCG2) and the multidrug resistance-associated protein 1 (MRP1, ABCC family).[1] A common feature of these transporters is that they use the energy of ATP hydrolysis to transport a wide variety of substrates out of cells against the concentration gradient. By actively effluxing substrates their intracellular concentrations are decreased thus leading to failure of chemotherapy.

Among the 49 identified human ABC-transporters the most intensively studied is P-gp. P-gp has the ability to transport a wide variety of structurally unrelated compounds out of the cells.[2] The protein is associated with poor bioavailability and fast drug elimination by influencing the drugs' pharmacokinetics.[3]

A most striking property of P-gp is the structural diversity of its substrates, among them many cytotoxic anticancer drugs like anthracyclines (doxorubicin, daunorubicin), taxanes (paclitaxel, docetaxel), podophyllotoxin derivatives (etoposid, teniposid), *Vinca* alkaloids (vinblastine, vincristine) and derivatives from *Camptothecа acuminata* (camptothecin, topotecan, irinotecan). A commonly accepted precondition is that P-gp substrates are amphipathic with a molecular mass between 400 and 1900 Da. In most cases anionic compounds do not interact with P-gp.[4,5]

Abbreviations: MDR, multidrug resistance; ABC, ATP-binding-cassette; P-gp, P-glycoprotein; BCRP, breast cancer-resistance protein; MRP, multidrug-resistance associated protein.

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Since the first report of MDR overcoming by the calcium channel blocker verapamil[6] a lot of effort has been invested in finding potent and specific P-gp inhibitors, called also MDR modulators. The 1st generation modulators (verapamil, cyclosporin A) are drugs which have been developed for treatment of other diseases. The use of these substances was limited due to their low efficacy and the required high doses associated with high toxicity. The second generation modulators (dexverapamil, PSC 833) possessed higher efficacy and lower toxicity, but when applied in patients serious drug–drug interactions have been observed due to the fact that both, the cytostatics and 2nd generations modulators are substrates of cytochrome P450 3A. In contrast to the 1st and 2nd generation modulators the 3rd generation modulators are not structurally related to or derived from existing drugs. They possess high efficacy, low toxicity and increased selectivity. Representatives of the 3rd generation modulators which are still under investigation are: tariquidar (XR9576), elacridar (GF120918), zosuquidar (LY335979), laniquidar (R1010933).[7] In early trials many of them showed promising activity; nevertheless these modulators failed later on due to observed toxicities or low survival advantage.[8] Thus to date, the search for new non-toxic, potent modulators lacking pharmacokinetic interactions is still in process.

XR9576 is one of most potent 3rd generation modulators. It belongs to a series of compounds based on the anthranilamide nucleus, called XR compounds, which have been developed and pharmacologically investigated by Xenova group Ltd.[9,10] The modulator contains a tetrahydroisoquinoline–ethyl-phenylamine substructure which is connected to a highly hydrophobic part via an amide bond.

XR9576 has also been used in our laboratory as a basis for a rational design of new MDR modulators[13]. Based on QSAR and molecular modelling studies of XR compounds important structural features and pharmacophore elements have been identified[11] that have been considered for synthesis of our new P-gp inhibitors. In contrast to the XR compounds, our compounds have smaller hydrophobic parts. Thus they are less lipophilic and have lower molecular weight. This could improve absorption and oral bioavailability. In this paper we describe the synthesis and biological evaluation of 39 newly synthesized compounds with MDR modulating activity. The compounds have been synthesized applying a general synthesis approach. In the structures the tetrahydroisoquinoline–ethyl-phenylamine scaffold is combined with the hydrophobic part using four different types of linkers. The P-gp inhibition activity of the compounds has been estimated by the functional calcein AM assay. Structure–activity relationship analysis revealed the structural elements and modifications that lead to an increased interaction with P-gp. Two promising inhibitors have been identified which are only three to fourfold less active than tariquidar. These compounds can serve as lead structures for the future development of new potent inhibitors of transport proteins involved in MDR.

2. Results and discussion

The general strategy used for synthesizing our P-gp related MDR modulators is shown in Scheme 1. Table 1 reports the structures and activity data of the 39 compounds.

All compounds possess a tetrahydroisoquinoline–phenylethylamine scaffold (**3a** or **3b**). The latter was obtained in two steps: (i) alkylation of the corresponding tetrahydroisoquinoline (**1a** or **1b**) with 1-(2-bromoethyl)-4-nitrobenzene leading to the intermediate products **2a** or **2b** followed by catalytic reduction of the nitro group yielding anilines **3a** or **3b**. (ii) Reaction of the anilines with the appropriate carboxylic acid chloride leading to the desired amide compounds **4**–**29**. Introduction of a urea linker instead of an amide group was achieved by reaction of the aniline with isocyanato-nitrobenzene. The nitro derivatives (**5a**, **5b**, **7a**, **7b**, **28**, 3**0a**, 3**0b**, **31**, **32**) were catalytically reduced to the corresponding amines (**6a**, **6b**, **8a**, **8b**, **29**, **33a**, **33b**, **34**, **35**). Two additional linker variations introduced amide-ether and amide-styryl groups (Scheme 1).

P-gp modulating activity of the synthesized compounds was evaluated by the calcein AM assay using P-gp overexpressing, adriamycin-resistant A2780adr cells.[12,13] As shown in different studies this cell line is supposed to express high levels of the ABCB1 gene product P-gp.[14–16] This has been confirmed by us applying different techniques. Gene expression was confirmed by RT-PCR analysis. [17] The expression of the protein was determined with a selective FITC-labelled P-gp antibody (17F9 monoclonal P-gp antibody) using flow cytometry. Additionally the drug-resistance factor against the cytotoxic drug doxorubicin was determined,[18] and found to be comparable with resistance factors reported in literature.[15] Further, inhibitory activities of nine structurally unrelated compounds were measured using MDCK cells transfected with ABCB1 gene (MDCK-MDR1). The excellent correlation with the calcein AM assay data obtained in A2780adr cells (Fig. 1) clearly emphasizes that P-gp is the main efflux mechanism influencing the calcein AM accumulation in these cells.

The inhibitory potencies varied greatly among the synthesized compounds. To classify the biological activities of the new inhibitors different standard modulators were investigated. We have chosen verapamil, diltiazem, and cyclosporin A as reference drugs representing the 1st generation modulators and tariquidar (XR9576) as a 3rd generation modulator (Table 1). As seen from the table the activity of the unsubstituted parent compound 4 (IC_{50} = 4.1 μM) is almost equal to that of verapamil (IC_{50} = 5.2 μM).

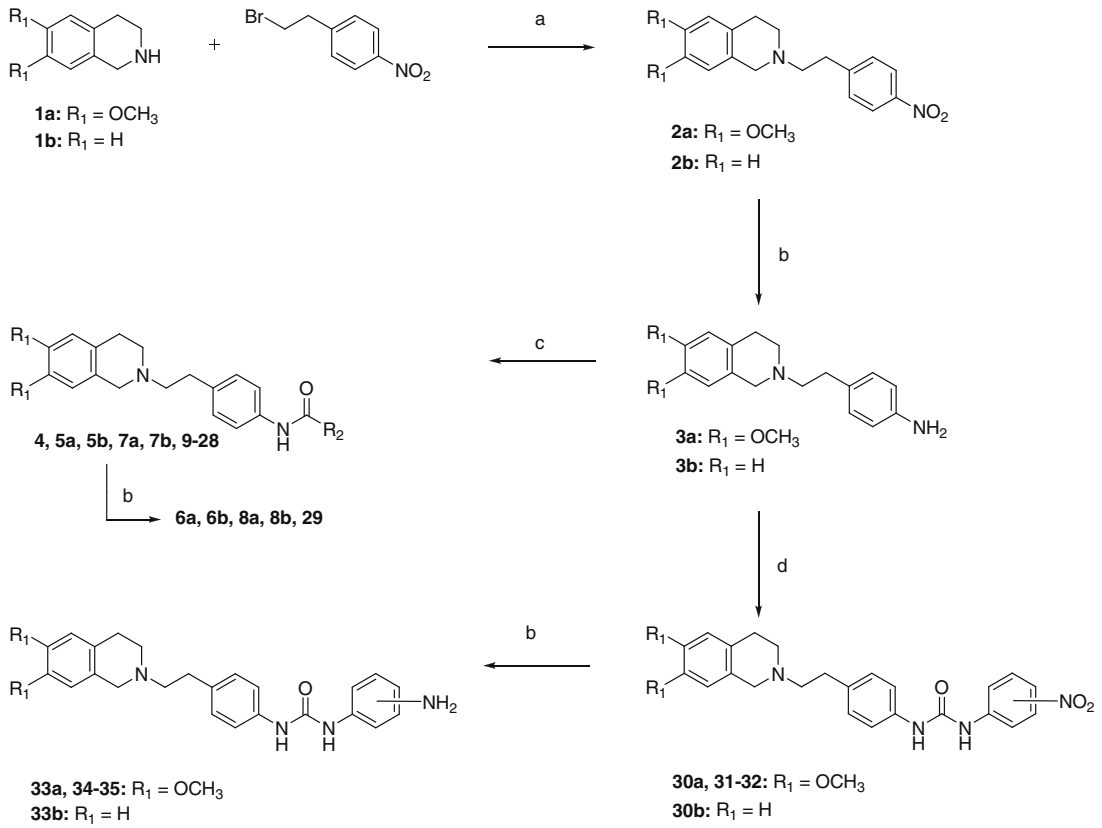
Comparing the activity data reported in Table 1 several conclusions about structure–activity relationships in the series can be drawn.

First, an addition of methoxy groups in positions 6 and 7 of the tetrahydroisoquinoline substructure (substituent R_1) leads to an increase of the inhibitory potencies compared to the corresponding unsubstituted derivatives. The positive contribution of the methoxy groups to the biological activities is obvious when comparing the IC_{50} values of **5a** (IC_{50} = 5.4 μM) and **5b** (IC_{50} = 14 μM), **7a** (IC_{50} = 1.4 μM) and **7b** (IC_{50} = 5.6 μM), **8a** (IC_{50} = 4.4 μM) and **8b** (IC_{50} = 12 μM) Therefore, the tetrahydroisoquinoline ring system supplemented with methoxy groups in position 6 and 7 was chosen as preferred template for the basic substructure; consequently, this structural element is present in most of the synthesized substances.

Next, an electron withdrawing nitro-substituent in *para* position of the phenyl ring system (compounds **7a** and **7b**) influences the inhibitory potency in a positive manner. Comparing the nitro-substituted derivatives **7a** (IC_{50} = 1.4) and **7b** (IC_{50} = 5.6) with the corresponding amino-compounds **8a** (IC_{50} = 4.4) **8b** (IC_{50} = 12) a two to three fold decrease in activity is apparent. When altering the position of the nitro group from *para* to *ortho* (substances **7a** and **5a**), the inhibitory potency decreases considerably, even below the level of the unsubstituted parent compound **4**.

A bromine substitutent at the phenyl ring (compounds **17**–**19**) has a small positive influence on P-gp inhibitory activity, regardless of the position of the bromine varying from *ortho* over *meta* to *para*. Interestingly, the hydrophilic and electron poor pyridyl derivative **16** is as active as the phenyl derivative **4**.

The inhibitory potency remains unchanged when methoxy groups in position 3 and 4 of the phenyl ring system (substituent R_2) are present (compare substances **4** and **20**). This is in contrast to anthranilamide MDR modulators where this structural modification leads to a twofold increase in activity.[9,11]



Scheme 1. Synthesis of tetrahydroisoquinoline–phenylethylamine based P-gp inhibitors with different linkers to the hydrophobic substituent R_2. Reagents and conditions: (a) K_2CO_3, CH_3CN, reflux, 24 h, (b) H_2, Pd/C, 4 bar, rt, 24 h, (c) R–COCl, THF, Et_3N, rt, 48 h, (d) R–NCO, THF, Et_3N, reflux, 6 h.

Extending the monocyclic to a bicyclic substituent the inhibitory potency is enhanced. Comparison of the IC_{50} values of the monocyclic derivatives **4** (IC_{50} = 4.1 μM) and **16** (IC_{50} = 4.8 μM) with their corresponding bicyclic analogues **15** (IC_{50} = 0.63 μM) and **9a** (IC_{50} = 0.57 μM) illustrates that this structural modification yields more effective inhibitors. Interestingly, the orientation of the bicyclic ring system is important for the biological activity as the IC_{50} values of the two different naphthyl derivatives indicate. The 2-naphthyl derivative (**15**) is two fold more active (IC_{50} = 0.63 μM) than the 1-naphthyl derivative (**14**) (IC_{50} = 1.4 μM). The decisive role of the orientation of the bicyclic ring system is even more obvious when comparing the IC_{50} values of the quinoline derivatives **9a** and **11**.

Among the investigated amide derivatives 3-quinolinyl and 2-quinoxalinyl derivatives are the most active compounds in accordance with the XR-compounds. Thus, the 3-quinolinyl, 2-quinoxalinyl and 2-naphthyl derivatives are promising lead structures. They are more than ten times more effective than verapamil and only four to six times less potent than tariquidar.

To investigate the role of the linker between the tetrahydroisoquinoline–phenylethylamine substructure and the hydrophobic part for the inhibitory potency the amide linker was replaced by different linker types.

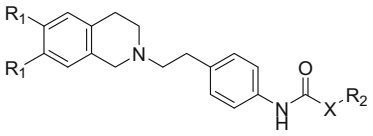
Eight derivatives with a urea linker have been synthesized. Among them compound **30a** with an *ortho*-nitro group has the lowest IC_{50} value (IC_{50} = 0.33 μM, Table 1). This substance is among the most active ones found in our library and is about 10-fold more potent than verapamil. As in the series of amide linked derivatives the removal of the two methoxy groups at the tetrahydroisoquinoline moiety leads to an approximately twofold decrease in activity (compound **30b** with IC_{50} of 0.77 μM). Regarding the effect of an *ortho*-nitro group on activity the linker type is decisive. The corresponding amide derivatives **5a** and **5b** show less inhibitory potencies than the parent compound **4**. Again the reduction of the nitro group to an amino group decreases activity (**33a**: IC_{50} = 21 μM and **33b**: IC_{50} = 19 μM)), and this activity decrease is much more pronounced in the urea series and relatively independent of the position of the amino group. Also the *para*-amino compound **35** (IC_{50} = 31 μM) is 20 times less active than the nitro-analogue (compound **32**, IC_{50} = 1.5 μM).

Extension of the amide linker by a methylenoxy group (**27**–**29**) proved to be an interesting and promising strategy for the design of new P-gp inhibitors. Among the three different amide-ether derivatives (**27**–**29**) compound **28** showed a superior inhibitory activity with an IC_{50} of 0.22 μM, highlighting this substance as the most active compound in our modulator library. Interestingly, the precondition for an enhanced interaction of substance **28** with P-gp is due to the nitro substituent in *ortho*-position. If the nitro group is absent or reduced to amino, the inhibitory potency considerably decreases. The amino derivative **29** is more than tenfold less active (IC_{50} = 3.4 μM) than the most effective modulator **28**.

Comparison of the biological activity of the amide derivative **4** (IC_{50} = 4.1 μM) with its corresponding amide-ether analogue **27** (IC_{50} = 3.1 μM) suggests that the length of the linker seems not to be decisive for the inhibitory potency. In this context the styryl derivatives (**23**–**26**) differ as elongation of the amide linker is related to a general increase of activity. The styryl derivative **23** (IC_{50} = 1.4 μM) is approximately three times more potent than its amide counterpart **4** (IC_{50} = 4.1 μM). Adding a chlorine substituent in *para* position (compound **25**) leads to a further twofold increase in activity (IC_{50} = 0.67 μM).

When comparing the influence of an *ortho*-nitro group on the activity in the four series a substantial difference becomes apparent. While in case of the amide and styryl linkers activities

Table 1
Structures of the compounds and their biological activity in the calcein AM assay.



Compound	R_1	R_2	X	IC_{50} ± SD (μM)
4	OCH_3	Phenyl	—	4.1 ± 1.2
5a	OCH_3	2-Nitrophenyl	—	5.4 ± 0.7
5b	H	2-Nitrophenyl	—	14 ± 3
6a	OCH_3	2-Aminophenyl	—	8.5 ± 1.6
6b	H	2-Aminophenyl	—	9.9 ± 4.7
7a	OCH_3	4-Nitrophenyl	—	1.4 ± 0.5
7b	H	4-Nitrophenyl	—	5.6 ± 2.7
8a	OCH_3	4-Aminophenyl	—	4.4 ± 2.8
8b	H	4-Aminophenyl	—	12 ± 3
9°	OCH_3	3-Quinolinyl	—	0.57 ± 0.18
9b	H	3-Quinolinyl	—	0.43 ± 0.11
10	OCH_3	2-Quinolinyl	—	0.85 ± 0.36
11	OCH_3	4-Quinolinyl	—	4.7 ± 0.7
12	OCH_3	6-Quinolinyl	—	0.65 ± 0.11
13	OCH_3	2-Quinoxalinyl	—	0.47 ± 0.05
14	OCH_3	1-Naphthyl	—	1.4 ± 0.4
15	OCH_3	2-Naphthyl	—	0.63 ± 0.18
16	OCH_3	3-Pyridyl	—	4.8 ± 1.5
17	OCH_3	2-Bromophenyl	—	3.3 ± 2.3
18	OCH_3	3-Bromophenyl	—	1.8 ± 0.2
19	OCH_3	4-Bromophenyl	—	2.4 ± 1.1
20	OCH_3	3,4-Dimethoxyphenyl	—	4.2 ± 2.1
21	OCH_3	4,5-Dimethoxy-2-nitrophenyl	—	13 ± 2
22	OCH_3	3,4-Methylendioxyphenyl	—	2.1 ± 0.5
23	OCH_3	Phenyl	–CH=CH–	1.4 ± 0.4
24	OCH_3	2-Nitrophenyl	–CH=CH–	1.1 ± 0.1
25	OCH_3	4-Chlorophenyl	–CH=CH–	0.67 ± 0.09
26	OCH_3	4,5-Dimethoxy-2-nitrophenyl	–CH=CH–	1.5 ± 0.4
27	OCH_3	Phenyl	$–CH_2–O–$	3.1 ± 0.1
28	OCH_3	2-Nitrophenyl	$–CH_2–O–$	0.22 ± 0.03
29	OCH_3	2-Aminophenyl	$–CH_2–O–$	3.4 ± 1.0
30a	OCH_3	2-Nitrophenyl	–NH–	0.33 ± 0.07
30b	H	2-Nitrophenyl	–NH–	0.77 ± 0.15
31	OCH_3	3-Nitrophenyl	–NH–	0.67 ± 0.20
32	OCH_3	4-Nitrophenyl	–NH–	1.5 ± 0.2
33a	OCH_3	2-Aminophenyl	–NH–	21 ± 3
33b	H	2-Aminophenyl	–NH–	19 ± 8
34	OCH_3	3-Aminophenyl	–NH–	14 ± 3
35	OCH_3	4-Aminophenyl	–NH–	31 ± 17
Tariquidar				0.078 ± 0.013
Diltiazem				49 ± 20
Verapamil				5.2 ± 2.0
Cyclosporin A				1.4 ± 0.3

Values are means with standard deviations from a minimum of three experiments.

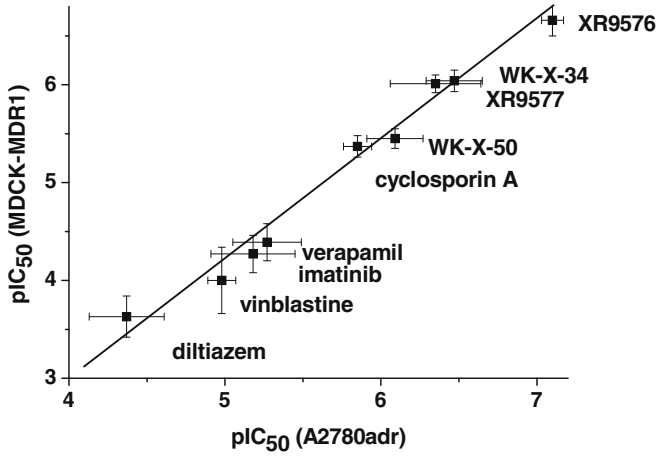


Figure 1. Scatterplot of the pIC_{50} values of nine structurally different compounds determined in the calcein AM assay using A2780adr and MDCK-MDR1 cells, respectively. Data shown are average ± SD of at least three independent experiments. The squared correlation coefficient is 0.98.

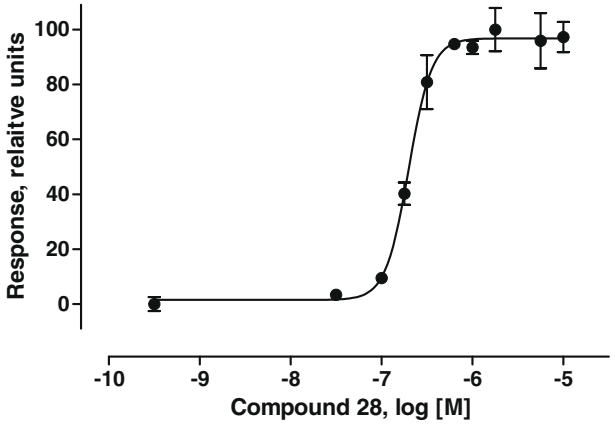


Figure 2. Concentration–response curve generated for compound **28** in A2780adr cells in the calcein AM assay: IC_{50} = 0.22 ± 0.03 μM (pIC_{50} = 6.65 ± 0.05). Data shown are average ± SD from one typical experiment with four replicates out of a series of six independent experiments.

of the unsubstituted and *ortho*-nitro derivatives are comparable, the nitro derivatives with urea (**30a**) and ether linker (**28**) are the most potent compounds. In order to elucidate the effect of the nitro group we performed a conformational analysis of the nitro derivatives and the unsubstituted compounds with the different linkers. To sample the conformational space 200 cycles of simulated annealing were performed for each compound and the obtained conformations of the molecules were then sorted by potential energy and compared. Besides the force field method the described conformers were subsequently optimized by the semiempirical method PM6 with MOPAC2007. The final conformations yielded 290 only marginal differences in the geometries. The most active compounds **28** and **30a**, although attached by different linkers in position X, share the same position of the hydrophobic part R_2 (Fig. 3). The amide group in **28** is flipped allowing the nitro group to form a hydrogen bond to the amide hydrogen. Also in case of the urea linker the planar conformation is stabilized by a hydrogen bond between the nitro group and the urea nitrogen. The ether attached unsubstituted compound **27** (purple) can adopt the same orientation of R_2 as the nitro substituted derivative **28**. But this conformation is less favored among the sampled conformations, probably because of the missing stabilizing hydrogen bond. The alignment of **28** with two other active pairs of less active compounds (the amides **4**, **5a** and the styryl derivatives **23**, **24**) is shown in Figure 4. None of those compounds can adopt a planar conformation similar to the most active compound **28**. Thus it can be speculated that the high activities of compounds **28** and **30a** can be explained by the position and planar orientation of the terminal aromatic substituent. Additionally, the electron withdrawing properties of substituents like the nitro group could positively contribute to the effect.

In summary, a number of new molecules have been synthesized on the basis of selected molecular features and subsequently tested as P-gp inhibitors. In the synthesized series a number of lead compounds were found that show P-gp inhibitory potency at submicromolar concentrations. This is a promising result compared to the activities of the standard inhibitors verapamil and cyclosporin A determined under the same conditions. The best compounds are about 10 times more active than verapamil and four times more active than cyclosporin A.

Figure 3. Superposition of the lowest energy conformations of the most active compounds **28** (purple) and **30a** (grey), showing that both compounds share the same position of the hydrophobic part in position R_2.

Figure 4. Superposition of lowest energy conformations of the most active compound **28** (purple) with the less active compounds **4**, **5a** and **23**, **24**; neither of these compounds can adopt the planar conformation of **28**.

Among the studied compounds the amide-ether derivative **28** possesses the strongest inhibitory potency against P-gp. Comparing its structure to that of tariquidar, compound **28** contains an elongated amide linker between the tetrahydroisoquinoline–phenylethylamine substructure and the hydrophobic part, but lacks the second amide linker present in the structure of tariquidar. In Figure 2 a typical concentration–response curve for compound **28** obtained with the calcein AM assay is shown (IC_{50} = 0.22 μM). This substance inhibits P-gp 20 times stronger than the 1st generation modulator verapamil and only three times less than the most potent modulator tariquidar (IC_{50} = 0.078 μM). Therefore, substance **28** could be classified as a promising candidate in our modulator library and will be used as a lead structure for synthesizing new effective P-gp modulators in future.

3. Experimental

3.1. General methods

Melting points were measured in open capillary tubes on a Gallenkamp melting point apparatus and are uncorrected. Spectral data were obtained on the following instruments: IR, Perkin–Elmer Paragon 1000; mass spectra, Kratos Concept 1-H, A.E.I.; ^{1}H NMR, Bruker Advance 500 (500 MHz); ^{13}C NMR, Bruker Advance 500 (125.8 MHz); chemical shifts are expressed in δ value (ppm) with using tetramethylsilan as an internal standard; multiplicity of resonance peaks is indicated as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). The marked protons (*) are exchangable with D_2O. The ^{13}C signals were assigned with the aid of distortionless enhancement by polarization transfer (DEPT) and twodimensional experiments (H–H COSY, C–H COSY), and classification of carbon atoms are indicated by CH_3 (primary), CH_2 (secondary), CH or Ar-CH (tertiary), or Ar-C (quarternary), the J values are in Hertz. Elemental analyses were performed on a Vario EL of Elementar. Found values were all within ±0.4% of the theoretical values except when indicated.

3.2. General procedure for the synthesis of the nitrophenylethylamines

3.2.1. 6,7-Dimethoxy-2-[2-(4-nitrophenyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (2a)

A mixture of 1-(2-bromoethyl)-4-nitrobenzene (10 mmol, 2.42 g), 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride (10.5 mmol, 2.41 g) and K_2CO_3 (25 mmol, 3.48 g) in 50 ml acetonitril was heated under reflux for 12 h. The solvent was evaporated, the residue taken up in 100 ml water and extracted three times with 75 ml DCM. The solution was dried over $MgSO_4$, filtered and concentrated. The product was recrystallized from ethanol to give yellow crystals: yield 2.6 g (73.7 %), mp 118 °C. ^{1}H NMR (DMSO-d_6): δ = 2.68 (m, 4H, 2 × CH_2), 2.72 (t, J = 7.6 Hz, 2H, CH_2), 2.96 (t, J = 7.3 Hz, 2H, CH_2), 3.52 (s, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 6.60 (s, 1H, ArH), 6.63 (s, 1H, ArH), 7.54 (d, J = 8.8 Hz, 2H, 2 × ArH), 8.13 (d, J = 8.8 Hz, 2H, 2 × ArH). ^{13}C NMR (DMSO-d_6): δ = 28.4 (CH_2), 32.7 (CH_2), 50.5 (CH_2), 55.1 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 58.5 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 123.3 (Ar-CH), 123.4 (2 × Ar-CH), 126.0 (Ar-C), 126.7 (Ar-C), 130.1 (2 × Ar-CH), 146.0 (Ar-C), 147.1 (Ar-C), 147.3 (Ar-C), 149.4 (Ar-C). Anal. Calcd for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.38; H, 6.46; N, 7.99.

3.2.2. 2-[2-(4-Nitrophenyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (2b)

The compound was prepared as described for the synthesis of (**2a**) starting from 1,2,3,4-tetrahydroisoquinoline (24.8 mmol, 3.3 g), 1-(2-bromoethyl)-4-nitrobenzene (20.6 mmol, 5.0 g) and K_2CO_3 (50 mmol, 6.96 g): yield 4.55 g (78.3%) of yellow crystals, mp 103 °C. ^{1}H NMR (DMSO-d_6): δ = 2.71–2.79 (m, 6H, 3 × CH_2), 2.97 (t, J = 7.3 Hz, 2H, CH_2), 3.61 (s, 2H, CH_2), 7.01 (m, 1H, ArH), 7.08 (m, 3H, 3 × ArH), 7.55 (d, J = 8.8 Hz, 2H, 2 × ArH), 8.13 (d, J = 8.8 Hz, 2H, 2 × ArH). ^{13}C NMR (DMSO-d_6): δ = 28.8 (CH_2), 32.6 (CH_2), 50.3 (CH_2), 55.5 (CH_2), 58.5 (CH_2), 123.4 (2 × Ar-CH), 125.6 (Ar-CH), 126.0 (Ar-CH), 126.5 (Ar-CH), 128.5 (Ar-CH), 130.1

(2 × Ar-CH), 134.3 (Ar-C), 135.0 (Ar-C), 146.0 (Ar-C), 149.4 (Ar-C). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.21; H, 6.41; N, 9.69.

3.3. General procedure for the hydrogenation

3.3.1. 4-[2-(6,7-Dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]phenylamine (3a)

10 mmol (3.42 g) of compound (**2a**) was dissolved in 200 ml ethanol and was hydrogenated at room temperature under 4 bar pressure in a Paar-apparatus in the presence of Pd/C as catalyst. After hydrogen absorption was completed, the catalyst was filtered off and the solution was concentrated to give 4-[2-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinoline-2-yl)-ethyl]-phenylamine as a white solid, yield 2.41 g (87%), mp 129 °C. ^{1}H NMR (DMSO-d_6): δ = 2.56 (m, 2H, CH_2), 2.62 (m, 4H, 2 × CH_2), 2.69 (t, J = 5.7 Hz, 2H, CH_2), 3.50 (s, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 4.78 (s, 2H*, NH_2), 6.48 (d, J = 8.5 Hz, 2H, 2 × ArH), 6.62 (s, 1H, ArH), 6.64 (s, 1H, ArH), 6.87 (d, J = 8.5 Hz, 2H, 2 × ArH). ^{13}C NMR (DMSO-d_6): δ = 28.5 (CH_2), 32.4 (CH_2), 50.8 (CH_2), 55.3 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 60.4 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 114.1 (2 × Ar-CH), 126.1 (Ar-C), 126.9 (Ar-C), 127.5 (Ar-C), 129.1 (2 × Ar-CH), 146.7 (Ar-C), 147.0 (Ar-C), 147.3 (Ar-C). Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 72.69; H, 7.68; N, 8.78.

3.3.2. 4-[2-(3,4-Dihydro-1*H*-isoquinolin-2-yl)ethyl]phenylamine (3b)

Following the procedure described for compound (**3a**), starting from (**2b**) (2.82 g, 10 mmol), compound (**3b**) (2.32 g, 92%) was obtained as a white solid, mp 90 °C. ^{1}H NMR (DMSO-d_6): δ = 2.58 (m, 2H, CH_2), 2.64 (m, 2H, CH_2), 2.68 (t, J = 5.8 Hz, 2H, CH_2), 2.78 (t, J = 5.8 Hz, 2H, CH_2), 3.58 (s, 2H, CH_2), 4.78 (s, 2H*, NH_2), 6.48 (d, J = 8.4 Hz, 2H, 2 × ArH), 6.88 (d, J = 8.4 Hz, 2H, 2 × ArH), 7.02–7.10 (m, 4H, 4 × ArH). ^{13}C NMR (DMSO-d_6): δ = 28.9 (CH_2), 32.4 (CH_2), 50.6 (CH_2), 55.6 (CH_2), 60.4 (CH_2), 114.1 (2 × Ar-CH), 125.5 (Ar-CH), 126.0 (Ar-CH), 126.5 (Ar-CH), 127.4 (Ar-C), 128.5 (Ar-CH), 129.1 (2 × Ar-CH), 134.3 (Ar-C), 135.1 (Ar-C), 146.7 (Ar-C). Anal. Calcd for $C_{17}H_{20}N_2 \cdot 0.2H_2O$: C, 79.77; H, 8.03; N, 10.94. Found: C, 79.71; H, 8.05; N, 10.83.

3.4. General procedure for the synthesis of the amides

3.4.1. *N*-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)benzamide (4)

5 mmol benzoylchloride was suspended in dry THF and added dropwise to a stirred solution of **3a** (5 mmol) and triethylamine (6 mmol) in dry THF at room temperature. The solution was stirred for 12 h. After the reaction was completed the solvent was removed in vacuum and the residue was treated with water and extracted three times with EtOAc. The organic phase was washed with dilute NaOH (1 N) and water, dried with $MgSO_4$, and concentrated. After recrystallization from DCM/*n*-hexane the compound was yielded as a white solid (66%), mp 233 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.94–3.19 (m, 8H, 4 × CH_2), 3.72 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 4.10 (s, 2H, CH_2), 6.73 (s, 1H, ArH), 6.76 (s, 1H, ArH), 7.26 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.52 (m, 2H, 2 × ArH), 7.57 (m, 1H, ArH), 7.74 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.96 (m, 2H, 2 × ArH), 10.24 (s, 1H*, NH). Anal. Calcd for $C_{26}H_{28}N_2O_3 \cdot 0.5H_2O$: C, 73.39; H, 6.87; N, 6.58. Found: C, 73.30; H, 6.76; N, 6.30.

3.4.2. *N*-{4-[2-(6,7-Dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)ethyl]phenyl}-2-nitrobenzamide (5a)

Following the procedure described for compound **4**, starting from **3a** and 2-nitrobenzoyl chloride, compound **5a** was obtained (78%) as a pale yellow solid, mp 184 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.67 (m, 6H, 3 × CH_2), 2.80 (t, 2H, CH_2), 3.53 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 6.63 (s, 1H, ArH), 6.65 (s, 1H, ArH), 7.23 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.56 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.74 (m, 2H, 2 × ArH), 7.85 (dt, J = 8.4 Hz, 1H, ArH), 8.12 (dd, J = 8.5 Hz, 1H, ArH), 10.55 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.4 (CH_2), 32.6 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 59.7 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 119.8 (2 × Ar-CH), 124.3 (Ar-CH), 126.1 (Ar-C), 126.8 (Ar-C), 129.1 (2 × Ar-CH), 129.4 (Ar-CH), 131.0 (Ar-CH), 132.9 (Ar-C), 134.1 (Ar-CH), 136.3 (Ar-C), 136.9 (Ar-C), 146.7 (Ar-C), 147.1 (Ar-C), 147.3 (Ar-C), 164.0 (CO). Anal. Calcd for $C_{26}H_{27}N_3O_5 \cdot 0.2H_2O$: C, 67.14; H, 5.94; N, 9.03. Found: C, 67.23; H, 5.91; N, 8.81.

3.4.3. *N*-{4-[2-(3,4-Dihydro-1*H*-isoquinolin-2-yl)ethyl]phenyl}-2-nitrobenzamide (5b)

Following the procedure described for compound **4**, starting from **3b** and 2-nitrobenzoyl chloride, compound **5b** was obtained (82%) as a white solid, mp 166 °C.

^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.70 (m, 4H, 2 × CH_2), 2.81 (m, 4H, 2 × CH_2), 3.63 (s, 2H, CH_2), 7.07 (m, 4H, 4 × ArH), 7.24 (d, J = 8.4 Hz, 2H, 2 × ArH), 7.57 (d, J = 8.4 Hz, 2H, 2 × ArH), 7.74 (m, 2H, 2 × ArH), 7.85 (d, J = 7.8 Hz, 1H, ArH), 8.12 (d, J = 7.6 Hz, 1H, ArH), 10.56 (s, 1H*, NH).

^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.8 (CH_2), 32.5 (CH_2), 50.5 (CH_2), 55.5 (CH_2), 59.7 (CH_2), 119.8 (2 × Ar-CH), 124.3 (Ar-CH), 125.6 (Ar-CH), 126.0 (Ar-CH), 126.5 (Ar-CH), 128.5 (Ar-CH), 129.1 (2 × Ar-CH), 129.4 (Ar-CH), 131.0 (Ar-CH), 132.9 (Ar-C), 134.1 (Ar-CH), 134.3 (Ar-C), 135.0 (Ar-C), 136.3 (Ar-C), 136.9 (Ar-C), 146.7 (Ar-C), 164.0 (CO). Anal. Calcd for $C_{24}H_{23}N_3O_3$: C, 71.80; H, 5.77; N, 10.47. Found: C, 71.46; H, 5.78; N, 10.40.

3.4.4. 2-Amino-*N*-{4-[2-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)ethyl]phenyl}benzamide (6a)

Following the procedure described for compound **3a**, starting from **5a** (1.58 g, 3.4 mmol), compound **6a** (89%) was obtained as a white solid, mp 150 °C.

^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.67 (m, 6H, 3 × CH_2), 2.78 (t, 2H, CH_2), 3.53 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 6.28 (s, 2H*, NH_2), 6.57 (d, J = 7.9 Hz, 1H, ArH), 6.62 (s, 1H, ArH), 6.64 (s, 1H, ArH), 6.73 (dd, J = 8.2 Hz, 1H, ArH), 7.18 (m, 3H, 3 × ArH), 7.59 (m, 3H, 3 × ArH), 9.89 (s, 1H*, NH).

^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.5 (CH_2), 32.6 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 59.7 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 114.8 (Ar-CH), 115.6 (Ar-C), 116.5 (Ar-CH), 120.7 (2 × Ar-CH), 126.1 (Ar-C), 126.9 (Ar-C), 128.8 (Ar-CH), 128.8 (2 × Ar-CH), 132.1 (Ar-CH), 135.7 (Ar-C), 137.2 (Ar-C), 147.1 (Ar-C), 147.3 (Ar-C), 149.8 (Ar-C), 167.8 (CO). Anal. Calcd for $C_{26}H_{29}N_3O_3 \cdot 0.2H_2O$: C, 71.77; H, 6.81; N, 9.66. Found: C, 71.81; H, 6.89; N, 9.48.

3.4.5. 2-Amino-*N*-{4-[2-(3,4-dihydro-1*H*-isoquinolin-2-yl)ethyl]phenyl}benzamide (6b)

Following the procedure described for compound **3a**, starting from **5b** (1.05 g, 2.5 mmol), compound **6b** (75%) was obtained as a white solid, mp 104 °C.

^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.69 (m, 6H, 3 × CH_2), 2.80 (t, 2H, CH_2), 3.62 (s, 2H, CH_2), 6.28 (s, 2H*, NH_2), 6.57 (m, 1H, ArH), 6.73 (dd, J = 8.4 Hz, 1H, ArH), 7.04 (m, 1H, ArH), 7.09 (m, 3H, 3 × ArH), 7.18 (m, 3H, 3 × ArH), 7.60 (m, 3H, 3 × ArH), 9.89 (s, 1H*, NH).

^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.9 (CH_2), 32.5 (CH_2), 50.6 (CH_2), 55.6 (CH_2), 59.7 (CH_2), 114.8 (Ar-CH), 115.6 (Ar-C), 116.5 (Ar-CH), 120.7 (2 × Ar-CH), 125.5 (Ar-CH), 126.0 (Ar-CH), 126.5 (Ar-CH), 128.5 (Ar-CH), 128.7 (Ar-CH), 128.8 (2 × Ar-CH), 132.1

(Ar-CH), 134.3 (Ar-C), 135.1 (Ar-C), 135.6 (Ar-C), 137.2 (Ar-C), 149.8 (Ar-C), 167.8 (CO). Anal. Calcd for $C_{24}H_{25}N_3O{\cdot}1.0C_2H_5OH$: C, 74.79; H, 7.48; N, 10.06. Found: C, 74.41; H, 7.44; N, 9.79.

3.4.6. *N*-{4-[2-(6,7-Dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)ethyl]phenyl}-4-nitrobenzamide (7a)

Following the procedure described for compound **4**, starting from **3a** and 4-nitrobenzoyl chloride, compound **7a** was obtained (88%) as a yellow solid, mp 134 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.67 (m, 6H, 3 × CH_2), 2.80 (t, 2H, CH_2), 3.53 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 6.62 (s, 1H, ArH), 6.64 (s, 1H, ArH), 7.25 (d, J = 8.8 Hz, 2H, 2 × ArH), 7.69 (d, J = 8.6 Hz, 2H, 2 × ArH), 8.16 (td, J = 8.8 Hz, 2H, 2 × ArH), 8.35 (td, J = 8.8 Hz, 2H, 2 × ArH), 10.46 (s, 1H*, NH).

^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.4 (CH_2), 32.6 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (2 × OCH_3), 59.6 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 120.6 (2 × Ar-CH), 123.6 (2 × Ar-CH), 129.0 (2 × Ar-CH), 129.3 (2 × Ar-CH), 126.1 (Ar-C), 126.8 (Ar-C), 136.6 (Ar-C), 136.7 (Ar-C), 147.1 (Ar-C), 147.3 (Ar-C), 149.2 (Ar-C), 163.8 (CO). Anal. Calcd for $C_{26}H_{27}N_3O_5$ $0.5H_2O$: C, 66.37; H, 6.00; N, 8.93. Found: C, 66.30; H, 5.94; N, 8.77.

3.4.7. *N*-{4-[2-(3,4-Dihydro-1*H*-isoquinolin-2-yl)ethyl]phenyl}-4-nitrobenzamide (7b)

Following the procedure described for compound **4**, starting from **3b** and 4-nitrobenzoyl chloride, compound **7b** was obtained (94%) as a yellow solid, mp 176 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.69 (m, 4H, 2 × CH_2), 2.80 (m, 4H, 2 × CH_2), 3.62 (s, 2H, CH_2), 7.03 (m, 1H, ArH), 7.08 (m, 3H, 3 × ArH), 7.25 (d, J = 8.7 Hz, 2H, 2 × ArH), 7.67 (m, 2H, 2 × ArH), 8.16 (ddd, J = 9 Hz, 2H, 2 × ArH), 8.35 (ddd, J = 9 Hz, 2H, 2 × ArH), 10.46 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 29.1 (CH_2), 32.8 (CH_2), 50.9 (CH_2), 55.9 (CH_2), 60.0 (CH_2), 121.2 (2 × Ar-CH), 124.2 (2 × Ar-CH), 126.1 (Ar-CH), 126.6 (Ar-CH), 127.0 (Ar-CH), 129.0 (Ar-CH), 129.5 (2 × Ar-CH), 129.7 (2 × Ar-CH), 134.7 (Ar-C), 135.3 (Ar-C), 136.8 (Ar-C), 137.2 (Ar-C), 141.2 (Ar-C), 149.7 (Ar-C), 164.6 (CO). Anal. Calcd for $C_{24}H_{23}N_3O_3{\cdot}0.2H_2O$: C, 71.16; H, 5.82; N, 10.37. Found: C, 71.14; H, 5.95; N, 10.36.

3.4.8. 4-Amino-*N*-(4-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)benzamide (8a)

Following the procedure described for compound **3a**, starting from **7a** (1.38 g, 3 mmol), compound **8a** (89%) was obtained as a light yellow solid, mp 128 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.67 (m, 6H, 3 × CH_2), 2.77 (t, 2H, CH_2), 3.53 (s, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 5.68 (s, 2H*, NH_2), 6.59 (td, J = 8.5 Hz, 2H, 2 × ArH), 6.62 (s, 1H, ArH), 6.64 (s, 1H, ArH), 7.17 (dd, J = 8.5 Hz, 2H, 2 × ArH), 7.63 (td, J = 8.5 Hz, 2H, 2 × ArH), 7.69 (td, J = 8.5 Hz, 2H, 2 × ArH), 9.65 (s, 1H*, NH).

^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.4 (CH_2), 32.6 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 59.8 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 112.7 (2 × Ar-CH), 120.3 (2 × Ar-CH), 126.1 (Ar-C), 126.9 (Ar-C), 128.7 (2 × Ar-CH), 129.4 (2 × Ar-CH), 135.1 (Ar-C), 137.8 (Ar-C), 147.1 (Ar-C), 147.3 (Ar-C), 152.2 (Ar-C), 165.3 (CO). Anal. Calcd for $C_{26}H_{29}N_3O_3$: C, 72.37; H, 6.77; N, 9.74. Found: C, 72.14; H, 6.78; N, 9.70.

3.4.9. 4-Amino-*N*-{4-[2-(3,4-dihydro-1*H*-isoquinolin-2-yl)ethyl]-phenyl}benzamide (8b)

Following the procedure described for compound **3a**, starting from **7b** (0.72 g, 1.8 mmol), compound **8b** (83%) was obtained as a white solid, mp 152 °C.^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.76 (m, 4H, 2 × CH_2), 2.90 (m, 4H, 2 × CH_2), 3.71 (s, 2H, CH_2), 4.01 (s, 2H*, NH_2), 6.65 (d, J = 8.7 Hz, 2H, 2 × ArH), 7.01 (m, 1H, ArH), 7.10 (m, 3H, 3 × ArH), 7.19 (d, J = 8.4 Hz, 2H, 2 × ArH), 7.51 (d, J = 8.4 Hz, 2H, 2 × ArH), 7.67 (d, J = 8.7 Hz, 2H, 2 × ArH), 7.74 (s, 1H*, NH).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 29.0 (CH_2), 33.3 (CH_2), 50.9 (CH_2), 56.0 (CH_2), 60.2 (CH_2), 114.2 (2 × Ar-CH), 120.3 (2 × Ar-CH), 124.2 (Ar-C), 125.6 (Ar-CH), 126.1 (Ar-CH), 126.6 (Ar-CH), 128.6 (Ar-CH), 128.8 (2 × Ar-CH), 129.2 (2 × Ar-CH), 134.2 (Ar-C), 134.6 (Ar-C), 136.1 (Ar-C), 136.4 (Ar-C), 149.9 (Ar-C), 165.4 (CO). Anal. Calcd for $C_{24}H_{25}N_3O{\cdot}0.8H_2O$: C, 74.95; H, 6.93; N, 10.93. Found: C, 74.77; H, 7.06; N, 10.24.

3.4.10. *N*-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)quinoline-3-carboxamide (9a)

Following the procedure described for compound **4**, starting from **3a** and quinoline-3-carbonyl chloride, compound **9a** (75%) was obtained as a white solid, mp 184 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.73–2.79 (m, 4H, 2 × CH_2), 2.83 (t, J = 5.5 Hz, 2H, CH_2), 2.89 (q, J = 5.5 Hz, 2H, CH_2), 3.63 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 6.52 (s, 1H, ArH), 6.58 (s, 1H, ArH), 7.23 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.59 (m, 3H, 3 × ArH), 7.79 (dt, J = 8.2 Hz, 1H, ArH), 7.86 (d, J = 8.2 Hz, 1H, ArH), 8.12 (d, J = 8.5 Hz, 1H, ArH), 8.19 (s, 1H*, NH), 8.63 (d, J = 2.2 Hz, 1H, ArH), 9.33 (d, J = 2.2 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 28.7 (CH_2), 33.5 (CH_2), 51.0 (CH_2), 55.7 (CH_2), 55.9 (OCH_3) 55.9 (OCH_3), 60.1 (CH_2), 109.5 (Ar-CH), 111.4 (Ar-CH), 120.7 (2 × Ar-CH), 126.1 (Ar-C), 126.5 (Ar-CH), 126.7 (Ar-CH), 126.8 (Ar-C), 127.5 (Ar-C), 127.6 (Ar-CH), 129.4 (Ar-CH), 129.4 (2 × Ar-CH), 131.4 (Ar-CH), 135.6 (Ar-C), 135.7 (Ar-CH), 137.3 (Ar-C), 147.2 (Ar-C), 147.5 (Ar-C), 148.1 (Ar-CH), 149.8 (Ar-C), 163.9 (CO). Anal. Calcd for $C_{29}H_{29}N_3O_3{\cdot}0.2H_2O$: C, 73.93; H, 6.29; N, 8.92. Found: C, 73.98; H, 6.21; N, 9.10.

3.4.11. *N*-(4-(2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)quinoline-3-carboxamide (9b)

Following the procedure described for compound **4**, starting from **3b** and quinoline-3-carbonyl chloride, compound **9b** (50%) was obtained as a white solid, mp 186 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.74–2.81 (m, 4H, 2 × CH_2), 2.88–2.93 (m, 4H, 2 × CH_2), 3.71 (s, 2H, CH_2), 7.01 (m, 1H, ArH), 7.10 (m, 3H, 3 × ArH), 7.24 (m, 2H, 2 × ArH), 7.59 (m, 3H, 3 × ArH), 7.79 (m, 1H, ArH), 7.87 (d, J = 7.9 Hz, 1H, ArH), 8.14 (d, J = 8.5 Hz, 1H, ArH), 8.16 (s, 1H*, NH), 8.63 (d, J = 2.2 Hz, 1H, ArH), 9.33 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 29.1 (CH_2), 33.4 (CH_2), 51.0 (CH_2), 56.1 (CH_2), 60.1 (CH_2), 120.7 (2 × Ar-CH), 125.8 (Ar-CH), 126.1 (Ar-CH), 126.6 (Ar-CH), 126.8 (Ar-C), 127.5 (Ar-C), 127.7 (Ar-CH), 128.6 (Ar-CH), 128.7 (Ar-CH), 129.4 (Ar-CH), 129.4 (2 × Ar-CH), 131.4 (Ar-CH), 134.2 (Ar-C), 134.6 (Ar-C), 135.6 (Ar-C), 135.7 (Ar-CH), 137.3 (Ar-C), 148.0 (Ar-CH), 149.8 (Ar-C), 163.9 (CO). Anal. Calcd for $C_{27}H_{25}N_3O$: C, 79.58; H, 6.18; N, 10.31. Found: C, 79.37; H, 6.14; N, 10.25.

3.4.12. *N*-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)isoquinoline-3-carboxamide (10)

Following the procedure described for compound **4**, starting from **3a** and quinoline-2-carbonyl chloride, compound **10** (38%) was obtained as a white solid, mp 141 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.67–2.72 (m, 6H, 3 × CH_2), 2.82 (t, 2H, CH_2), 3.55 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 6.63 (s, 1H, ArH), 6.65 (s, 1H, ArH), 7.28 (d, J = 8.2 Hz, 2H, 2 × ArH), 7.75 (t, J = 7.4 Hz, 1H, ArH), 7.84 (d, J = 8.2 Hz, 2H, 2 × ArH), 7.91 (t, J = 7.6 Hz, 1H, ArH), 8.11 (d, J = 7.9 Hz, 1H, ArH), 8.24 (q, 2H, 2 × ArH), 8.61 (d, J = 8.5 Hz, 1H, ArH), 10.63 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.4 (CH_2), 32.6 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 59.6 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 118.8 (Ar-CH), 120.4 (2 × Ar-CH), 126.1 (Ar-C), 126.8 (Ar-C), 128.2 (Ar-CH), 128.4 (Ar-CH), 129.0 (Ar-C), 129.0 (2 × Ar-CH), 129.4 (Ar-CH), 130.8 (Ar-CH), 136.3 (Ar-C), 136.4 (Ar-C), 138.3 (Ar-CH), 146.0 (Ar-C), 147.1 (Ar-C), 147.3 (Ar-C),

150.3 (Ar-C), 162.6 (CO). Anal. Calcd for $C_{29}H_{29}N_3O_3 \cdot 0.5H_2O$: C, 73.09; H, 6.35; N, 8.82. Found: C, 73.00; H, 6.05; N, 9.20.

3.4.13. *N*-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)quinoline-4-carboxamide (11)

Following the procedure described for compound **4**, starting from **3a** and quinoline-4-carbonyl chloride, compound **11** (55%) was obtained as a white solid, mp 199 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.66–2.71 (m, 6H, 3 × CH_2), 2.82 (t, J = 7.5 Hz, 2H, CH_2), 3.54 (s, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 6.63 (s, 1H, ArH), 6.65 (s, 1H, ArH), 7.26 (d, J = 8.6 Hz, 2H, 2 × ArH), 7.67 (m, 4H, 4 × ArH), 7.82 (dt, J = 5.5 Hz, 1H, ArH), 8.13 (d, J = 8.7 Hz, 2H, 2 × ArH), 9.02 (d, J = 4.4 Hz, 1H, ArH), 10.66 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.4 (CH_2), 32.6 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 59.6 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 119.3 (Ar-CH), 120.1 (2 × Ar-CH), 124.2 (Ar-C), 125.4 (Ar-CH), 126.1 (Ar-C), 126.8 (Ar-C), 127.7 (Ar-CH), 129.1 (2 × Ar-CH), 129.6 (Ar-C), 130.0 (Ar-CH), 136.6 (Ar-C), 136.8 (Ar-C), 142.2 (Ar-C), 147.1 (Ar-C), 147.3 (Ar-C), 148.1 (Ar-C), 150.4 (Ar-CH), 165.2 (CO). Anal. Calcd for $C_{29}H_{29}N_3O_3 \cdot 0.8H_2O$: C, 72.27; H, 6.40; N, 8.72. Found: C, 72.09; H, 6.29; N, 8.60.

3.4.14. *N*-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)quinoline-6-carboxamide (12)

Following the procedure described for compound **4**, starting from **3a** and quinoline-6-carbonyl chloride, compound **12** (56%) was obtained as a light yellow solid, mp 177 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.65–2.73 (m, 6H, 3 × CH_2), 2.81 (t, J = 7.7 Hz, 2H, CH_2), 3.54 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 6.63 (s, 1H, ArH), 6.65 (s, 1H, ArH), 7.25 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.62 (q, J = 4.2 Hz, 1H, ArH), 7.72 (d, J = 8.5 Hz, 2H, 2 × ArH), 8.12 (d, J = 8.9 Hz, 1H, ArH), 8.25 (d, J = 8.5, 1.9 Hz, 1H, ArH), 8.51 (m, 1H, ArH), 8.62 (d, J = 2.2 Hz, 1H, ArH), 9.00 (q, J = 2.0 Hz, 1H, ArH), 10.42 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.4 (CH_2), 32.6 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 59.7 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 120.6 (2 × Ar-CH), 122.4 (Ar-CH), 126.1 (Ar-C), 126.8 (Ar-C), 127.2 (Ar-CH), 128.2 (Ar-C), 128.5 (Ar-CH), 128.9 (2 × Ar-CH), 129.2 (Ar-CH), 133.0 (Ar-C), 136.1 (Ar-C), 137.1 (Ar-C), 137.3 (Ar-CH), 147.1 (Ar-C), 147.3 (Ar-C), 148.9 (Ar-C), 152.3 (Ar-CH), 165.0 (CO). Anal. Calcd for $C_{29}H_{29}N_3O_3 \cdot 0.2H_2O$: C, 73.93; H, 6.29; N, 8.92. Found: C, 73.76; H, 6.45; N, 8.84.

3.4.15. *N*-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)quinoxaline-2-carboxamide (13)

Following the procedure described for compound **4**, starting from **3a** and quinoxaline-2-carbonyl chloride, compound **13** (41%) was obtained as a white solid, mp 150 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.67–2.72 (m, 6H, 3 × CH_2), 2.82 (t, 2H, CH_2), 3.54 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 6.63 (s, 1H, ArH), 6.65 (s, 1H, ArH), 7.28 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.83 (d, J = 8.9 Hz, 2H, 2 × ArH), 8.01 (m, 2H, 2 × ArH), 8.22 (m, 1H, ArH), 8.29 (m, 1H, ArH), 9.54 (s, 1H, ArH), 10.72 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.4 (CH_2), 32.6 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 59.6 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 120.7 (2 × Ar-CH), 126.1 (Ar-C), 126.8 (Ar-C), 129.0 (2 × Ar-CH), 129.3 (Ar-C), 129.7 (Ar-C), 131.5 (Ar-C), 132.2 (Ar-CH), 136.2 (Ar-C), 136.7 (Ar-C), 139.8 (Ar-C), 143.1 (Ar-C), 144.1 (Ar-CH), 144.9 (Ar-C), 147.1 (Ar-C), 147.3 (Ar-C), 161.9 (CO). Anal. Calcd for $C_{28}H_{28}N_4O_3 \cdot 0.2H_2O$: C, 71.23; H, 6.06; N, 11.87. Found: C, 70.95; H, 5.83; N, 11.84.

3.4.16. *N*-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)-1-naphthamide (14)

Following the procedure described for compound **4**, starting from **3a** and 1-naphthoyl chloride, compound **14** (70%) was obtained as a white solid, mp 151 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.70–2.88 (m, 8H, 4 × CH_2), 3.64 (s, 2H, CH_2), 3.70 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 6.65 (s, 1H, ArH), 6.67 (s, 1H, ArH), 7.25 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.58 (m, 3H, 3 × ArH), 7.72 (d, J = 7.9 Hz, 3H, 3 × ArH), 8.01 (m, 1H, ArH), 8.06 (d, J = 8.2 Hz, 1H, ArH), 8.16 (t, J = 4.9 Hz, 1H, ArH), 10.48 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.0 (CH_2), 32.2 (CH_2), 50.8 (CH_2), 55.1 (CH_2), 55.7 (OCH_3) 55.7 (OCH_3), 59.3 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 120.0 (2 × Ar-CH), 125.2 (Ar-CH), 125.3 (Ar-CH), 125.5 (Ar-CH), 125.8 (Ar-C), 126.5 (Ar-CH), 127.1 (Ar-CH), 128.4 (Ar-CH), 129.0 (2 × Ar-CH), 129.8 (Ar-C), 130.1 (Ar-CH), 133.3 (Ar-C), 135.0 (Ar-C), 135.6 (Ar-C), 137.5 (Ar-C), 147.2 (Ar-C), 147.5 (Ar-C), 167.3 (CO). Anal. Calcd for $C_{30}H_{30}N_2O_3 \cdot 0.2H_2O$: C, 76.64; H, 6.52; N, 5.96. Found: C, 76.35; H, 6.65; N, 5.87.

3.4.17. *N*-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)-2-naphthamide (15)

Following the procedure described for compound **4**, starting from **3a** and 2-naphthoyl chloride, compound **15** (73%) was obtained as a white solid, mp 155 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.64–2.74 (m, 6H, 3 × CH_2), 2.81 (t, J = 7.6 Hz, 2H, CH_2), 3.54 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 6.63 (s, 1H, ArH), 6.65 (s, 1H, ArH), 7.24 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.62 (m, 2H, 2 × ArH), 7.72 (d, J = 8.6 Hz, 2H, 2 × ArH), 8.02 (m, 4H, 4 × ArH), 8.56 (s, 1H, ArH), 10.33 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.5 (CH_2), 32.6 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 59.7 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 120.5 (2 × Ar-CH), 124.6 (Ar-CH), 126.1 (Ar-C), 126.9 (Ar-C), 126.9 (Ar-CH), 127.8 (Ar-CH), 127.9 (Ar-CH), 128.0 (Ar-CH), 128.1 (Ar-CH), 128.9 (2 × Ar-CH), 129.0 (Ar-CH), 132.2 (Ar-C), 132.5 (Ar-C), 134.4 (Ar-C), 136.0 (Ar-C), 137.3 (Ar-C), 147.1 (Ar-C), 147.3 (Ar-C), 165.5 (CO). Anal. Calcd for $C_{30}H_{30}N_2O_3 \cdot 0.2H_2O$: C, 76.64; H, 6.52; N, 5.96. Found: C, 76.79; H, 6.45; N, 6.01.

3.4.18. *N*-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)nicotinamide (16)

Following the procedure described for compound **4**, starting from **3a** and nicotinoyl chloride, compound **16** (59%) was obtained as a yellow solid, mp 71 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.64–2.71 (m, 6H, 3 × CH_2), 2.80 (t, 2H, CH_2), 3.53 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 6.62 (s, 1H, ArH), 6.64 (s, 1H, ArH), 7.24 (td, J = 8.5 Hz, 2H, 2 × ArH), 7.55 (m, 1H, ArH), 7.67 (td, J = 8.5 Hz, 2H, 2 × ArH), 8.28 (m, 1H, ArH), 8.74 (q, J = 2.1 Hz, 1H, ArH), 9.09 (q, J = 2.2 Hz, 1H, ArH), 10.36 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.4 (CH_2), 32.6 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 59.7 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 120.5 (2 × Ar-CH), 123.6 (Ar-CH), 126.1 (Ar-C), 126.8 (Ar-C), 128.9 (2 × Ar-CH), 130.7 (Ar-C), 135.5 (Ar-CH), 136.3 (Ar-C), 136.9 (Ar-C), 147.1 (Ar-C), 147.3 (Ar-C), 148.8 (Ar-CH), 152.1 (Ar-CH), 164.0 (CO). Anal. Calcd for $C_{25}H_{27}N_3O_3 \cdot 0.5H_2O$: C, 70.40; H, 6.62; N, 9.85. Found: C, 70.27; H, 6.96; N, 9.52.

3.4.19. 2-Bromo-*N*-(4-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)benzamide (17)

Following the procedure described for compound **4**, starting from **3a** and 2-bromobenzoyl chloride, compound **17** (77%) was obtained as a light yellow solid, mp 158 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.64–2.71 (m, 6H, 3 × CH_2), 2.79 (t, 2H, CH_2), 3.53 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 6.62 (s, 1H, ArH), 6.65 (s, 1H, ArH), 7.21 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.40 (dt, J = 7.9 Hz, 1H, ArH), 7.49 (m, 2H, 2 × ArH), 7.61 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.69 (d, J = 7.9 Hz, 1H, ArH), 10.35 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.4 (CH_2), 32.6 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 59.7 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 119.1 (Ar-C), 119.7 (2 × Ar-CH), 126.1 (Ar-C),

126.8 (Ar-C), 127.8 (Ar-CH), 128.9 (Ar-CH), 129.0 (2 × Ar-CH), 131.2 (Ar-CH), 132.8 (Ar-CH), 136.1 (Ar-C), 137.0 (Ar-C), 139.4 (Ar-C), 147.1 (Ar-C), 147.3 (Ar-C), 165.7 (CO). Anal. Calcd for $C_{26}H_{27}BrN_2O_3 \cdot 0.33\ H_2O$: C, 62.28; H, 5.56; N, 5.59. Found: C, 62.00; H, 5.38; N, 5.99.

3.4.20. 3-Bromo-*N*-(4-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)benzamide (18)

Following the procedure described for compound **4**, starting from **3a** and 3-bromobenzoyl chloride, compound **18** (69%) was obtained as a pale yellow solid, mp 230 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.93–3.07 (m, 4H, 2 × CH_2), 3.15–3.28 (m, 4H, 2 × CH_2), 3.72 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 4.11 (s, 2H, CH_2), 6.73 (s, 1H, ArH), 6.76 (s, 1H, ArH), 7.27 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.49 (t, J = 7.9 Hz, 1H, ArH), 7.72 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.78 (m, 1H, ArH), 7.96 (dt, J = 8.2 Hz, 1H, ArH), 8.14 (t, J = 1.9 Hz, 1H, ArH), 10.35 (s, 1H*, NH). Anal. Calcd for $C_{26}H_{27}BrN_2O_3 \cdot 0.2H_2O$: C, 62.58; H, 5.53; N, 5.61. Found: C, 62.54; H, 5.59; N, 5.55.

3.4.21. 4-Bromo-*N*-(4-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)benzamide (19)

Following the procedure described for compound **4**, starting from **3a** and 4-bromobenzoyl chloride, compound **19** (74%) was obtained as a white solid, mp 183 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.76 (m, 4H, 2 × CH_2), 2.83 (t, 2H, CH_2), 2.88 (q, 2H, CH_2), 3.63 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.52 (s, 1H, ArH), 6.58 (s, 1H, ArH), 7.21 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.52 (d, J = 8.2 Hz, 2H, 2 × ArH), 7.57 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.70 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.85 (s, 1H*, NH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 28.6 (CH_2), 33.4 (CH_2), 51.0 (CH_2), 55.7 (CH_2), 55.9 (OCH_3) 55.9 (OCH_3), 60.1 (CH_2), 109.5 (Ar-CH), 111.4 (Ar-CH), 120.5 (2 × Ar-CH), 126.1 (Ar-C), 126.4 (Ar-C), 126.5 (Ar-C), 128.6 (2 × Ar-CH), 129.3 (2 × Ar-CH), 132.0 (2 × Ar-CH), 133.8 (Ar-C), 135.7 (Ar-C), 137.0 (Ar-C), 147.2 (Ar-C), 147.5 (Ar-C), 164.7 (CO). Anal. Calcd for $C_{26}H_{27}BrN_2O_3 \cdot 0.5H_2O$: C, 61.91; H, 5.60; N, 5.55. Found: C, 61.58; H, 5.43; N, 5.59.

3.4.22. *N*-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)-3,4-dimethoxybenzamide (20)

Following the procedure described for compound **4**, starting from **3a** and 3,4-dimethoxybenzoyl chloride, compound **20** (55%) was obtained as a white solid, mp 181 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.66–2.82 (m, 8H, 4 × CH_2), 3.57 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.63 (s, 1H, ArH), 6.65 (s, 1H, ArH), 7.06 (d, J = 8.5 Hz, 1H, ArH), 7.21 (d, J = 8.2 Hz, 2H, 2 × ArH), 7.52 (d, J = 1.9 Hz, 1H, ArH), 7.60 (dd, J = 8.2 Hz, J = 1.9 Hz, 1H, ArH), 7.65 (d, J = 8.5 Hz, 2H, 2 × ArH), 9.97 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.3 (CH_2), 32.4 (CH_2), 50.9 (CH_2), 55.1 (CH_2), 55.6 (OCH_3), 55.7 (OCH_3), 55.8 (OCH_3), 55.8 (OCH_3), 59.5 (CH_2), 110.2 (Ar-CH), 111.1 (Ar-CH), 111.3 (Ar-CH), 112.0 (Ar-CH), 120.7 (2 × Ar-CH), 121.1 (Ar-CH), 126.0 (Ar-C), 126.6 (Ar-C), 127.2 (Ar-C), 128.8 (2 × Ar-CH), 135.5 (Ar-C), 137.3 (Ar-C), 147.1 (Ar-C), 147.4 (Ar-C), 148.5 (Ar-C), 151.7 (Ar-C), 164.9 (CO). Anal. Calcd for $C_{28}H_{32}N_2O_5 \cdot 0.67H_2O$: C, 68.83; H, 6.88; N, 5.73. Found: C, 68.78; H, 6.94; N, 6.07.

3.4.23. *N*-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)-4,5-dimethoxy-2-nitrobenzamide (21)

Following the procedure described for compound **4**, starting from **3a** and 4,5-dimethoxy-2-nitrobenzoyl chloride, compound **21** (66%) was obtained as a pale yellow solid, mp 152 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.64–2.70 (m, 6H, 3 × CH_2), 2.79 (t, J = 7.5 Hz, 2H, CH_2), 3.62 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.62 (s, 1H, ArH), 6.64 (s, 1H, ArH), 7.22 (t, 3H, 3 × ArH), 7.56 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.68 (s, 1H, ArH), 10.38 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.4 (CH_2), 32.6 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3), 55.7 (OCH_3), 56.5 (OCH_3), 56.8 (OCH_3), 59.7 (CH_2), 107.4 (Ar-CH), 110.2 (Ar-CH), 111.2 (Ar-CH), 112.0 (Ar-CH), 119.7 (2 × Ar-CH), 126.1 (Ar-C), 126.9 (Ar-C), 127.6 (Ar-CH), 129.0 (2 × Ar-CH), 136.1 (Ar-C), 137.1 (Ar-C), 138.9 (Ar-C), 147.1 (Ar-C), 147.3 (Ar-C), 149.1 (Ar-C), 153.2 (Ar-C), 164.0 (CO). Anal. Calcd for $C_{28}H_{31}N_3O_7 \cdot 0.33H_2O$: C, 63.75; H, 6.05; N, 7.96. Found: C, 63.66; H, 5.86; N, 7.98.

3.4.24. *N*-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)benzo[*d*][1,3]-dioxole-5-carboxamide (22)

Following the procedure described for compound **4**, starting from **3a** and benzo[*d*][1,3]dioxole-5-carbonyl chloride, compound **22** (80%) was obtained as a white solid, mp 180 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.66–2.71 (m, 6H, 3 × CH_2), 2.78 (t, J = 7.5 Hz, 2H, CH_2), 3.56 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 6.11 (s, 2H, CH_2), 6.62 (s, 1H, ArH), 6.64 (s, 1H, ArH), 7.03 (d, J = 8.2 Hz, 1H, ArH), 7.20 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.50 (d, J = 1.5 Hz, 1H, ArH), 7.56 (dd, J = 8.2 Hz, 1H, ArH), 7.64 (d, J = 8.5 Hz, 2H, 2 × ArH), 9.96 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.3 (CH_2), 32.5 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 59.6 (CH_2), 101.9 (CH_2), 107.8 (Ar-CH), 108.0 (Ar-CH), 110.2 (Ar-CH), 112.0 (Ar-CH), 120.5 (2 × Ar-CH), 122.9 (Ar-CH), 126.0 (Ar-C), 126.6 (Ar-C), 128.8 (2 × Ar-CH), 129.0 (Ar-C), 135.7 (Ar-C), 137.3 (Ar-C), 147.1 (Ar-C), 147.5 (Ar-C), 147.7 (Ar-C), 150. 1 (Ar-C), 164.4 (CO). Anal. Calcd for $C_{27}H_{28}N_2O_5 \cdot 0.2H_2O$: C, 69.87; H, 6.17; N, 6.04. Found: C, 69.93; H, 6.22; N, 6.02.

3.4.25. *N*-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)cinnamamide (23)

Following the procedure described for compound **4**, starting from **3a** and cinnamoyl chloride, compound **23** (38%) was obtained as a pale yellow solid, mp 150 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.69–2.83 (m, 8H, 4 × CH_2), 3.61 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 6.64 (s, 1H, ArH), 6.66 (s, 1H, ArH), 6.83 (d, J = 15.5 Hz, 1H, CO–*CH*=CH), 7.21 (d, J = 8.6 Hz, 2H, 2 × ArH), 7.41 (m, 3H, 3 × ArH), 7.56 (d, J = 15.8 Hz, 1H, Ar-*CH*=CH), 7.61 (m, 4H, 4 × ArH), 10.14 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.1 (CH_2), 32.2 (CH_2), 50.6 (CH_2), 54.9 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 59.3 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 119.4 (2 × Ar-CH), 122.6 (CO-*CH*=CH), 125.8 (Ar-C), 126.1 (Ar-C), 127.8 (2 × Ar-CH), 129.1 (2 × Ar-CH), 129.1 (2 × Ar-CH), 129.8 (Ar-CH), 134.9 (Ar-C), 135.3 (Ar-C), 137.4 (Ar-C), 140.0 (Ar-*CH*=CH), 147.1 (Ar-C), 147.4 (Ar-C), 163.5 (CO). Anal. Calcd for $C_{28}H_{30}N_2O_3 \cdot 0.4H_2O$: C, 74.77; H, 6.90; N, 6.23. Found: C, 74.48; H, 7.20; N, 6.61.

3.4.26. (*E*)-*N*-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)-3-(2-nitrophenyl)acrylamide (24)

Following the procedure described for compound **4**, starting from **3a** and (*E*)-3-(2-nitrophenyl)acryloyl chloride, compound **24** (72%) was obtained as a pale yellow solid, mp 169 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.64–2.72 (m, 6H, 3 × CH_2), 2.79 (m, J = 8.6 Hz, 2H, CH_2), 3.53 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 6.62 (s, 1H, ArH), 6.64 (s, 1H, ArH), 6.81 (d, J = 15.8 Hz, 1H, CO-*CH*=CH), 7.22 (d, J = 8.6 Hz, 2H, 2 × ArH), 7.60 (d, J = 8.6 Hz, 2H, 2 × ArH), 7.65 (m, 1H, ArH), 7.81 (m, 2H, 2 × ArH), 7.83 (d, J = 15.8 Hz, 1H, Ar-*CH*=CH), 8.06 (d, J = 7.9 Hz, 1H, ArH), 10.25 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.4 (CH_2), 32.6 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 59.6 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 119.5 (2 × Ar-CH), 124.8 (CO-*CH*=CH), 126.1 (Ar-C), 126.8 (Ar-C), 127.3 (Ar-CH), 128.9 (Ar-CH), 129.1 (2 × Ar-CH), 130.1 (Ar-C), 130.5 (Ar-CH), 134.0 (Ar-CH), 135.0 (Ar-*CH*=CH), 136.0 (Ar-C), 137.0 (Ar-C), 147.1 (Ar-C),

147.3 (Ar-C), 148.4 (Ar-C), 162.7 (CO). Anal. Calcd for $C_{28}H_{29}N_3O_5 \cdot 0.5H_2O$: C, 67.73; H, 6.09; N, 8.46. Found: C, 67.69; H, 5.86; N, 8.49.

3.4.27. (*E*)-3-(4-Chlorophenyl)-*N*-(4-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)acrylamide (25)

Following the procedure described for compound **4**, starting from **3a** and (*E*)-3-(4-chlorophenyl)acryloyl chloride, compound **25** (28%) was obtained as a pale grey solid, mp 198 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.64–2.70 (m, 6H, 3 × CH_2), 2.78 (t, 2H, CH_2), 3.53 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 6.62 (s, 1H, ArH), 6.64 (s, 1H, ArH), 6.78 (d, J = 15.5 Hz, 1H, CO-*C*H=CH), 7.20 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.48–7.64 (m, 7H, 6 × ArH, 1 × Ar-*C*H=CH), 10.11 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.4 (CH_2), 32.5 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 59.6 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 119.4 (2 × Ar-CH), 123.4 (CO-*C*H=CH), 126.1 (Ar-C), 126.8 (Ar-C), 129.1 (2 × Ar-CH), 129.2 (2 × Ar-CH), 129.5 (2 × Ar-CH), 133.9 (Ar-C), 134.2 (Ar-C), 135.7 (Ar-C), 137.2 (Ar-C), 138.6 (Ar-*C*H=CH), 147.1 (Ar-C), 147.3 (Ar-C), 163.2 (CO). Anal. Calcd for $C_{28}H_{29}ClN_2O_3 \cdot 0.5H_2O$: C, 69.20; H, 6.22, Cl, 7.29; N, 5.76. Found: C, 69.16; H, 6.38; N, 5.70.

3.4.28. (*E*)-3-(4,5-Dimethoxy-2-nitrophenyl)-*N*-(4-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)-acrylamide (26)

Following the procedure described for compound **4**, starting from **3a** and (*E*)-3-(4,5-dimethoxy-2-nitrophenyl)acryloyl chloride, compound **26** (84%) was obtained as a yellow solid, mp 184 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.64–2.70 (m, 6H, 3 × CH_2), 2.78 (t, J = 7.5 Hz, 2H, CH_2), 3.53 (s, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.62 (s, 1H, ArH), 6.64 (s, 1H, ArH), 6.78 (d, J = 15.5 Hz, 1H, ArH), 7.20 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.26 (s, 1H, ArH), 7.60 (d, J = 8.9 Hz, 2H, 2 × ArH), 7.65 (s, 1H, ArH), 7.90 (d, J = 15.5 Hz, 1H, ArH), 10.21 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.4 (CH_2), 32.6 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 56.3 (OCH_3) 56.4 (OCH_3), 59.6 (CH_2), 108.1 (Ar-CH), 110.1 (Ar-CH), 110.2 (Ar-CH), 112.0 (Ar-CH), 119.4 (2 × Ar-CH), 124.7 (Ar-C), 126.1 (CH), 126.1 (Ar-C), 126.8 (Ar-C), 129.1 (2 × Ar-CH), 135.4 (CH), 135.8 (Ar-C), 137.1 (Ar-C), 141.2 (Ar-C), 147.1 (Ar-C), 147.3 (Ar-C), 149.4 (Ar-C), 153.0 (Ar-C), 162.9 (CO). Anal. Calcd for $C_{30}H_{33}N_3O_7 \cdot 0.75H_2O$: C, 64.22; H, 6.20; N, 7.49. Found: C, 64.01; H, 5.97; N, 7.44.

3.4.29. *N*-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)-2-phenoxyacetamide (27)

Following the procedure described for compound **4**, starting from **3a** and 2-phenoxyacetyl chloride, compound **27** (44%) was obtained as a pale white solid, mp 122 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.66–2.80 (m, 8H, 4 × CH_2), 3.57 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 4.66 (s, 2H, OCH_2), 6.63 (s, 1H, ArH), 6.65 (s, 1H, ArH), 6.98 (m, 3H, 3 × ArH), 7.19 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.30 (m, 2H, 2 × ArH), 7.54 (d, J = 8.5 Hz, 2H, 2 × ArH), 9.95 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.2 (CH_2), 32.3 (CH_2), 50.6 (CH_2), 55.0 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 59.4 (CH_2), 67.3 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 114.8 (2 × Ar-CH), 119.9 (2 × Ar-CH), 121.3 (Ar-CH), 125.9 (Ar-C), 126.4 (Ar-C), 129.0 (2 × Ar-CH), 129.6 (2 × Ar-CH), 135.8 (Ar-C), 136.5 (Ar-C), 147.1 (Ar-C), 147.4 (Ar-C), 158.0 (Ar-C), 166.5 (CO). Anal. Calcd for $C_{27}H_{30}N_2O_4 \cdot 0.75H_2O$: C, 70.49; H, 6.90; N, 6.09. Found: C, 70.35; H, 7.06; N, 5.88.

3.4.30. *N*-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)-2-(2-nitrophenoxy)acetamide (28)

Following the procedure described for compound **4**, starting from **3a** and 2-(2-nitrophenoxy)acetyl chloride, compound **28** (81%) was obtained as a white solid, mp 131 °C. MS m/z 492.2 (MH^+, 60), 307.1 (18), 289.1 (10), 206.2 (100), 165.1 (11). ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.62–2.69 (m, 6H, 3 × CH_2), 2.77 (t, J = 7.7 Hz, 2H, CH_2), 3.51 (s, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 4.90 (s, 2H, OCH_2), 6.61 (s, 1H, ArH), 6.64 (s, 1H, ArH), 7.15 (dt, J = 8.2 Hz, 1H, ArH), 7.20 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.28 (d, J = 8 Hz, 1H, ArH), 7.48 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.64 (m, 1H, ArH), 7.91 (dd, J = 8.2 Hz, 1H, ArH), 9.95 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.4 (CH_2), 32.5 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 59.7 (CH_2), 68.0 (OCH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 115.6 (Ar-CH), 119.5 (2 × Ar-CH), 121.4 (Ar-CH), 125.4 (Ar-CH), 126.1 (Ar-C), 126.9 (Ar-C), 129.1 (2 × Ar-CH), 134.7 (Ar-CH), 136.2 (Ar-C), 136.2 (Ar-C), 139.6 (Ar-C), 147.1 (Ar-C), 147.3 (Ar-C), 151.0 (Ar-C), 165.4 (CO). Anal. Calcd for $C_{27}H_{29}N_3O_6 \cdot 0.2H_2O$: C, 65.49; H, 5.98; N, 8.49. Found: C, 65.55; H, 6.07; N, 8.47.

3.4.31. *N*-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)-2-(2-aminophenoxy)acetamide (29)

Following the procedure described for compound **3a**, starting from **28** (1.03 g, 2.1 mmol), compound **29** (89%) was obtained as a white solid, mp 163 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.62–2.70 (m, 6H, 3 × CH_2), 2.78 (t, J = 7.7 Hz, 2H, CH_2), 3.52 (s, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 4.59 (s, 2H, OCH_2), 5.03 (s, 2H*, NH_2), 6.49 (m, 1H, ArH), 6.62 (s, 1H, ArH), 6.64 (s, 1H, ArH), 6.66 (dd, J = 6 Hz, 1H, ArH), 6.72 (dt, J = 7.2 Hz, 1H, ArH), 6.81 (dd, J = 8.2 Hz, 1H, ArH), 7.20 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.53 (d, J = 8.5 Hz, 2H, 2 × ArH), 9.86 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.4 (CH_2), 32.6 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 59.7 (CH_2), 68.1 (OCH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 112.9 (Ar-CH), 114.6 (Ar-CH), 116.2 (Ar-CH), 120.6 (2 × Ar-CH), 122.2 (Ar-CH), 126.1 (Ar-C), 126.9 (Ar-C), 128.9 (2 × Ar-CH), 136.1 (Ar-C), 136.3 (Ar-C), 138.4 (Ar-C), 145.0 (Ar-C), 147.1 (Ar-C), 147.3 (Ar-C), 166.8 (CO). Anal. Calcd for $C_{27}H_{31}N_3O_4$: C, 70.26; H, 6.77; N, 9.10. Found: C, 70.03; H, 6.93; N, 9.03.

3.4.32. 1-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)-3-(2-nitrophenyl)urea (30a)

3 mmol of 1-isocyanato-2-nitrobenzene was suspended in dry THF and added dropwise to a stirred solution of **3a** (3 mmol) in 50 ml of dry THF at room temperature. After a few minutes catalytic amounts of triethylamine was added and the solution was refluxed for 6 h. After the reaction was completed the solvent was removed in vacuo. To the residue 50 ml of water was added and extracted three times with EtOAc. The organic phase was dried with $MgSO_4$, and concentrated. Recrystallization from DCM/*n*-hexane the compound **30a** was yielded as a yellow solid (71%), mp 167 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.62–2.70 (m, 6H, 3 × CH_2), 2.76 (t, J = 7.5 Hz, 2H, CH_2), 3.52 (s, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 6.61 (s, 1H, ArH), 6.64 (s, 1H, ArH), 7.18 (m, 3H, 3 × ArH), 7.38 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.67 (dt, J = 8.5 Hz, 1H, ArH), 8.07 (dd, J = 8.2 Hz, 1H, ArH), 8.29 (dd, J = 8.5 Hz, 1H, ArH), 9.56 (s, 1H*, NH), 9.73 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.4 (CH_2), 32.5 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 59.7 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 118.9 (2 × Ar-CH), 122.2 (Ar-CH), 122.6 (Ar-CH), 125.5 (Ar-CH), 126.1 (Ar-C), 126.8 (Ar-C), 129.1 (2 × Ar-CH), 134.8 (Ar-C), 135.1 (Ar-CH), 135.2 (Ar-C), 137.1 (Ar-C), 137.7 (Ar-C), 147.0 (Ar-C), 147.3 (Ar-C), 151.9 (CO). Anal. Calcd for $C_{26}H_{28}N_4O_5$: C, 65.53; H, 5.92; N, 11.76. Found: C, 65.32; H, 6.06; N, 11.61.

3.4.33. 1-(4-(2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)-3-(2-nitrophenyl)urea (30b)

Following the procedure described for compound **30a**, starting from **3b** and 1-isocyanato-2-nitrobenzene, compound **30b** (85%)

was obtained as a yellow solid, mp 157 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.75 (m, 2H, CH_2), 2.80 (t, 2H, CH_2), 2.87–2.93 (m, 4H, 2 × CH_2), 3.70 (s, 2H, CH_2), 7.00–7.11 (m, 5H, 5 × ArH), 7.21 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.32 (m, 3H, 2 × ArH, NH*), 7.56 (m, 1H, ArH), 8.13 (d, J = 8.5 Hz, 1H, ArH), 8.64 (d, J = 8.5 Hz, 1H, ArH), 9.91 (s, 1H*, NH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 29.0 (CH_2), 33.3 (CH_2), 51.0 (CH_2), 56.0 (CH_2), 60.1 (CH_2), 121.8 (Ar-CH), 121.8 (2 × Ar-CH), 122.2 (Ar-CH), 125.6 (Ar-CH), 125.7 (Ar-CH), 126.1 (Ar-CH), 126.6 (Ar-CH), 128.7 (Ar-CH), 129.6 (2 × Ar-CH) 134.2 (Ar-C), 134.6 (Ar-C), 135.1 (Ar-C), 135.8 (Ar-CH), 135.9 (Ar-C), 136.4 (Ar-C), 137.4 (Ar-C), 152.5 (CO). Anal. Calcd for $C_{24}H_{24}N_4O_3 \cdot 0.5H_2O$: C, 67.75; H, 5.92; N, 13.17. Found: C, 67.96; H, 5.90; N, 13.34.

3.4.34. 1-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)-3-(3-nitrophenyl)urea (31)

Following the procedure described for compound **30a**, starting from **3a** and 1-isocyanato-3-nitrobenzene, compound **31** (93%) was obtained as a yellow solid, mp 166 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.62–2.70 (m, 6H, 3 × CH_2), 2.76 (t, J = 7.6 Hz, 2H, CH_2), 3.52 (s, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 6.62 (s, 1H, ArH), 6.64 (s, 1H, ArH), 7.13 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.37 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.54 (t, J = 8.2 Hz, 1H, ArH), 7.69 (dd, J = 8.2 Hz, 1H, ArH), 7.79 (dd, J = 8.2 Hz, 1H, ArH), 8.54 (t, J = 2.2 Hz, 1H, ArH), 8.75 (s, 1H*, NH), 9.19 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.5 (CH_2), 32.5 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 59.6 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 112.2 (Ar-CH), 116.4 (Ar-CH), 118.9 (2 × Ar-CH), 124.4 (Ar-CH), 126.1 (Ar-C), 126.9 (Ar-C), 129.1 (2 × Ar-CH), 130.1 (Ar-CH), 134.6 (Ar-C), 137.2 (Ar-C), 141.3 (Ar-C), 147.0 (Ar-C), 147.3 (Ar-C), 148.3 (Ar-C), 152.6 (CO). Anal. Calcd for $C_{26}H_{28}N_4O_5 \cdot 0.67H_2O$: C, 63.92; H, 6.05; N, 11.47. Found: C, 63.79; H, 6.26; N, 11.25.

3.4.35. 1-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)-3-(4-nitrophenyl)urea (32)

Following the procedure described for compound **30a**, starting from **3a** and 1-isocyanato-4-nitrobenzene, compound **32** (90%) was obtained as a yellow solid, mp 138 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.62–2.70 (m, 6H, 3 × CH_2), 2.76(t, J = 7.5, 2H, CH_2), 3.52 (s, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 6.62 (s, 1H, ArH), 6.64 (s, 1H, ArH), 7.17 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.37 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.67 (d, J = 9.5 Hz, 2H, 2 × ArH), 8.16 (d, J = 9.5 Hz, 2H, 2 × ArH), 8.84 (s, 1H*, NH), 9.41 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.4 (CH_2), 32.5 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3), 55.7 (OCH_3), 59.7 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 117.5 (2 × Ar-CH), 118.9 (2 × Ar-CH), 125.3 (2 × Ar-CH), 126.1 (Ar-C), 126.9 (Ar-C), 129.1 (2 × Ar-CH), 134.8 (Ar-C), 137.0 (Ar-C), 141.1 (Ar-C), 146.6 (Ar-C), 147.1 (Ar-C), 147.3 (Ar-C), 152.1 (CO). Anal. Calcd for $C_{26}H_{28}N_4O_5 \cdot 1.0H_2O$: C, 63.15; H, 6.11; N, 11.33. Found: C, 63.15; H, 6.23; N, 11.03.

3.4.36. 1-(2-Aminophenyl)-3-(4-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)-phenyl)urea (33a)

Following the procedure described for compound **3a**, starting from **30a** (0.95 g, 2 mmol), compound **31a** (88%) was obtained as a light yellow solid, mp 171 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.63–2.76 (m, 8H, 4 × CH_2), 3.53 (s, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 4.74 (s, 2H*, NH_2), 6.56 (dt, J = 7.9 Hz, 1H, ArH), 6.62 (s, 1H, ArH), 6.64 (s, 1H, ArH), 6.72 (dd, J = 7.9 Hz, 1H, ArH), 6.82 (dt, J = 7.9 Hz, 1H, ArH), 7.13 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.33 (m, 3H, 3 × ArH), 7.70 (s, 1H*, NH), 8.65 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.4 (CH_2), 32.4 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 59.8 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 116.0 (Ar-CH), 117.0 (Ar-CH), 118.2 (2 × Ar-CH), 123.7 (Ar-CH), 124.4 (Ar-CH), 125.0 (Ar-C), 126.1 (Ar-C), 126.8 (Ar-C), 129.0 (2 × Ar-CH), 133.6 (Ar-C), 138.1 (Ar-C), 140.9 (Ar-C), 147.1 (Ar-C), 147.3 (Ar-C), 153.3 (CO). Anal. Calcd for $C_{26}H_{30}N_4O_3 \cdot 0.2H_2O$: C, 69.37; H, 6.81; N, 12.45. Found: C, 69.27; H, 6.90; N, 12.34.

3.4.37. 1-(2-Aminophenyl)-3-(4-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)urea (33b)

Following the procedure described for compound **3a**, starting from **30b** (0.84 g, 2 mmol), compound **33b** (58%) was obtained as white solid, mp 176 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.66 (m, 2H, CH_2), 2.71 (d, J = 5.8 Hz, 2H, CH_2), 2.75–2.81 (m, 4H, 2 × CH_2), 3.58 (s, 2H, CH_2), 4.73 (s, 2H*, NH_2), 6.56 (dt, J = 7.6 Hz, 1H, ArH), 6.72 (dd, J = 7.6 Hz, 1H, ArH), 6.82 (dt, J = 7.6 Hz, 1H, ArH), 7.03 (m, 1H, ArH), 7.09 (m, 3H, 3 × ArH), 7.14 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.33 (m, 3H, 3 × ArH), 7.67 (s, 1H*, NH), 8.62 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.6 (CH_2), 32.4 (CH_2), 50.5 (CH_2), 55.6 (CH_2), 59.8 (CH_2), 116.0 (Ar-CH), 117.0 (Ar-CH), 118.2 (2 × Ar-CH), 123.7 (Ar-CH), 124.4 (Ar-CH), 125.0 (Ar-C), 125.5 (Ar-CH), 126.0 (Ar-CH), 126.5 (Ar-CH), 128.5 (Ar-CH), 129.0 (2 × Ar-CH) 133.6 (Ar-CH), 134.3 (Ar-C), 135.1 (Ar-C), 138.1 (Ar-C), 140.9 (Ar-C), 153.3 (CO). Anal. Calcd for $C_{24}H_{26}N_4O$: C, 74.58; H, 6.78; N, 14.50. Found: C, 74.25; H, 6.62; N, 14.87.

3.4.38. 1-(3-Aminophenyl)-3-(4-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)-phenyl)urea (34)

Following the procedure described for compound **3a**, starting from **31** (0.95 g, 2 mmol), compound **34** (81%) was obtained as a white solid, mp 172 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.61–2.75 (m, 8H, 4 × CH_2), 3.52 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 4.97 (s, 2H*, NH_2), 6.17 (d, J = 7.9 Hz, 1H, ArH), 6.53 (d, J = 8.2 Hz, 1H, ArH), 6.62 (s, 1H, ArH), 6.64 (s, 1H, ArH), 6.75 (s, 1H, ArH), 6.87 (t, 1H, J = 7.9 Hz, ArH), 7.13 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.32 (d, J = 8.5 Hz, 2H, 2 × ArH), 8.28 (s, 1H*, NH), 8.43 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.4 (CH_2), 32.5 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3) 55.7 (OCH_3), 59.8 (CH_2), 103.9 (Ar-CH), 106.2 (Ar-CH), 108.2 (Ar-CH), 110.2 (Ar-CH), 112.0 (Ar-CH), 118.2 (2 × Ar-CH), 126.1 (Ar-C), 126.9 (Ar-C), 129.0 (2 × Ar-CH), 129.1 (Ar-CH), 133.8 (Ar-C), 137.9 (Ar-C), 140.5 (Ar-C), 147.1 (Ar-C), 147.3 (Ar-C), 149.2 (Ar-C), 152.6 (CO). Anal. Calcd for $C_{26}H_{30}N_4O_3 \cdot ?H_2O$: C, 69.00; H, 6.83; N, 12.38. Found: C, 68.75; H, 6.76; N, 12.38.

3.4.39. 1-(4-Aminophenyl)-3-(4-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)-phenyl)urea (35)

Following the procedure described for compound **3a**, starting from **32** (0.95 g, 2 mmol), compound **35** (76%) was obtained as a light yellow solid, mp 187 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.61–2.75 (m, 8H, 4 × CH_2), 3.52 (s, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 4.72 (s, 2H*, NH_2), 6.50 (d, J = 8.8 Hz, 2H, 2 × ArH), 6.62 (s, 1H, ArH), 6.64 (s, 1H, ArH), 7.05 (d, J = 8.8 Hz, 2H, 2 × ArH), 7.11 (d, J = 8.5 Hz, 2H, 2 × ArH), 7.31 (d, J = 8.5 Hz, 2H, 2 × ArH), 8.07 (s, 1H*, NH), 8.35 (s, 1H*, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 28.4 (CH_2), 32.5 (CH_2), 50.7 (CH_2), 55.2 (CH_2), 55.6 (OCH_3), 55.7 (OCH_3), 59.9 (CH_2), 110.2 (Ar-CH), 112.0 (Ar-CH), 114.3 (2 × Ar-CH), 118.2 (2 × Ar-CH), 120.8 (2 × Ar-CH), 126.1 (Ar-C), 126.9 (Ar-C), 128.8 (Ar-C), 129.0 (2 × Ar-CH), 133.5 (Ar-C), 138.2 (Ar-C), 144.1 (Ar-C), 147.1 (Ar-C), 147.3 (Ar-C), 153.1 (CO). Anal. Calcd for $C_{26}H_{30}N_4O_3 \cdot 0.4H_2O$: C, 68.82; H, 6.84; N, 12.35. Found: C, 68.76; H, 6.69; N, 12.23.

3.5. Calcein AM assay

Cells were grown under standard conditions in T75- or T175-flasks. After reaching confluence of approximately 80%, cells were harvested by short trypsination (0.05 % trypsin/0.02 % EDTA). Pel-

leted cells were resuspended in fresh culture medium and counted with a Casy I Modell TT cell counter (Schaerfe System GmbH, Reutlingen, Germany). Cells were washed three times with Krebs-HEPES buffer, and then seeded into colourless 96 well plates (Greiner, Frickenhausen, Germany) at a density of approximately 30,000 cells in a volume of 90 μl per well. Then, 10 μl of the test compounds were added, resulting in a final volume of 100 μl per well. The prepared 96 well plates were preincubated for 30 min. After the preincubation period, 33 μl of a 1.25 μM Calcein AM solution which was protected from light were added to each well.

The fluorescence was measured immediately in constant time intervals (120 s) up to 46 min using an excitation wavelength of 485 nm and an emission wavelength of 520 nm with a BMG POLARstar microplate reader tempered at 37 °C.

3.6. Conformational analysis

As no X-ray data on the compounds were available the energy minimum conformers of the compounds were generated from their sketched and minimized structures (MOE MMFF94x, 0.05 kcal mol^{-1} $Å^{-1}$ gradient, MMFF94x charges) using simulated annealing (Sybyl MMFF94 force field). Simulated annealing was performed for 200 cycles, 1000 K initial temperature for heating for 2000 fs equilibration, 0 K target temperature for 10,000 fs annealing time, and exponential annealing function. The 200 local minima obtained were then optimized by the MMFF94x force field in MOE.

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