Bioorganic & Medicinal Chemistry 21 (2013) 6053–6062

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

N-Methylanilide and *N*-methylbenzamide derivatives as phosphodiesterase 10A (PDE10A) inhibitors

John Paul Kilburn [a,*], Jan Kehler [a], Morten Langgård [a], Mette N. Erichsen [b], Sebastian Leth-Petersen [b], Mogens Larsen [c], Claus Tornby Christoffersen [d], Jacob Nielsen [e]

[a] H. Lundbeck A/S, Department of Medicinal Chemistry, DK-2500 Valby, Denmark
[b] Department of Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Copenhagen, DK-2100 Copenhagen, Denmark
[c] LEO Pharma A/S, Department of Medicinal Chemistry, DK-2750 Ballerup, Denmark
[d] H. Lundbeck A/S, Department of Molecular Pharmacology, DK-2500 Valby, Denmark
[e] H. Lundbeck A/S, Department of Molecular Neurobiology, DK-2500 Valby, Denmark

ARTICLE INFO

Article history:
Received 29 April 2013
Revised 9 July 2013
Accepted 12 July 2013
Available online 23 July 2013

Keywords:
Phosphodieasterase 10A inhibitors
Schizophrenia
Antipsychotics
Molecular modeling
MPO

ABSTRACT

PDE10A is a recently identified phosphodiesterase with a quite remarkable localization since the protein is abundant only in brain tissue. Based on this unique localization, research has focused extensively on using PDE10A modulators as a novel therapeutic approach for dysfunction in the basal ganglia circuit including Parkinson's disease, Huntington's disease, schizophrenia, addiction and obsessive compulsive disorder. Medicinal chemistry efforts identified the *N*-methyl-*N*-[4-(quinolin-2-ylmethoxy)-phenyl]-isonicotinamide (**8**) as a nanomolar PDE10A inhibitor. A subsequent Lead-optimization program identified analogous *N*-methylanilides and their corresponding *N*-methylbenzamides (**29**) as potent PDE10A inhibitors, concurrently some interesting and unexpected binding modes were identified.

1. Introduction

The cyclic nucleotides cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are ubiquitous intracellular messengers responsible for mediation of the biological response of a variety of extracellular signals, including hormones, light and neurotransmitters.[1] In neurons, the response includes the activation of cAMP- and cGMP-dependent kinases and subsequent phosphorylation of proteins involved in acute regulation of synaptic transmission as well as in neuronal differentiation and survival.[2,3]

The phosphodiesterases (PDEs) are a family of bimetallic hydrolase enzymes that inactivate cAMP/cGMP by catalytic hydrolysis of the 3′-ester bond, forming the inactive 5′-monophosphate.[1,3] Phosphodiesterase 10A (PDE10A) is a basal ganglia specific hydrolase that can degrade both cAMP and cGMP. Based on the unique localization of PDE10A with predominant expression in the medium spiny neurons of the striatal complex, research has focused on the use of PDE10A modulators as a novel therapeutic approach for diseases with dysfunction in the basal ganglia circuit including Parkinson's disease, Huntington's disease, schizophrenia, addiction and obsessive compulsive disorder.[4]

Early studies on the relative selective PDE inhibitor papaverine (Fig. 1) indicated a possible link between antipsychotic activity and PDE10A inhibition.[4d,8] Subsequent studies have yielded several new compound classes that selectively inhibit PDE10A, notably MP-10 (**3**, Fig. 1), which is currently under clinical evaluation for

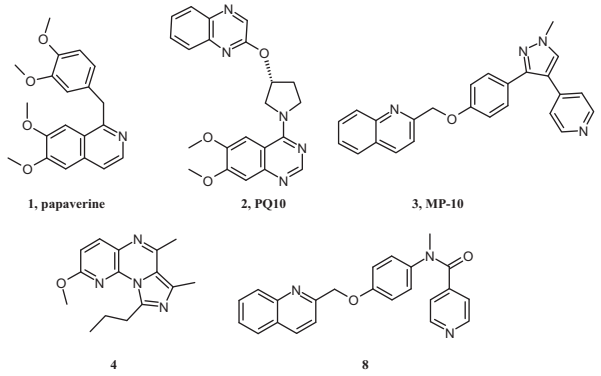


Figure 1. Some published PDE10A inhibitors **1**,[4d] **2**,[5b] **3**,[6] **4**,[7] and the novel *N*-methylanilide lead **8**.

* Corresponding author. Tel.: +45 30833215.
E-mail address: jpk@lundbeck.com (J.P. Kilburn).

0968-0896/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmc.2013.07.030

the treatment of schizophrenia.[4,5] Preclinical evidence suggests that a PDE10A inhibitor could provide anti-psychotic, pro-cognitive and negative symptom efficacy.[4,5]

In our search for PDE10A inhibitors, we decided to investigate the possibilities of identifying chemotypes with an MP10-like structure and binding properties. In our pursuit we discovered that substituted *N*-methylanilides were potent and selective inhibitors of PDE10A. The first compound **8** (Fig. 1, Table 1) was a PDE10A inhibitor with similar potency as papaverine. Compound **8** was an attractive starting point for several reasons: it was metabolically stable (HClint 1.1 L/min, human liver blood flow = 1.4 L/min), it had no Herg activity (IC_{50} >50 μM), it had a good selectivity for PDE10A compared to other PDEs (PDEx >50), good penetration into the brain (B/P rat = 0.6) and it showed in vivo activity in a model for antipsychotic activity with a potency (ED_{50} = 60 mg/kg) similar to that of papaverine. However, **8** was considered to lack potency when compared to MP-10, which in the same antipsychotic model exhibits an ED_{50} of 1.8 mg/kg.

A recent report[9] on the correlation between physical chemical properties and CNS druglike molecules has suggested the multiparameter optimization (MPO) algorithm to predict the correlation between physico-chemical properties and CNS druglike properties based on historical compounds. Compounds are rated on a scale from one to six, above four being a good score. The algorithm is based on six physicochemical parameters: lipophilicity in form of the calculated partition coefficient (*c*Log*P*), the calculated distribution coefficient (*c*Log*D*) at pH 7.4, molecular weight (MW), topological polar surface area (TPSA), number of hydrogen bond donors (HBD) and the most basic center (pK_a). A lead optimization program founded on compound **8** was initiated with the aim of increasing potency and using the MPO algorithm as a tool for selection of compounds.

2. Results and discussion

Synthesis protocols employed for substituted *N*-methylanilides are outlined in Scheme 1.

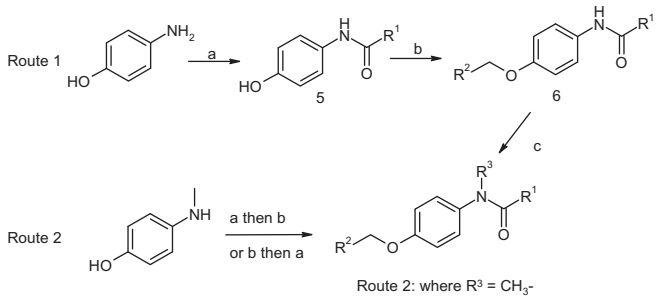
In one approach (Route 1), O-alkylation of starting material 4-aminophenol employing standard Williamson's ether synthesis conditions yielded anilines **5**. Acylation of **5** employing acid chlorides or carboxylic acids under standard amide bond forming conditions, yielded anilides of general formula **6** and final compound **7**. N-alkylation using alkyl iodides and sodium hydride as base yielded the final compounds. In a second approach (Route 2) *N*-methyl-4-aminophenol (R^3 = methyl) was acylated then O-alkylated as previously described. The sequence of these two reactions could be reversed depending on the focus of compound generation to yield the objective *N*-methylanilides.

Preliminary investigations were directed towards the role of R^3, while R^1 and R^2 were held constant as the 4-pyridyl (R^1) and 2-quinoline (R^2), respectively. Interestingly the secondary amide analogue **7** with R^3 = H was markedly less potent than the original hit **8**. Similarly, the ethyl- and butyl-analogues **9** and **10** had diminished affinities (Table 2).

Table 1
IC_{50} of compounds **1**, **2**, **3**, **4** and **8** for the inhibition of PDE10A enzyme

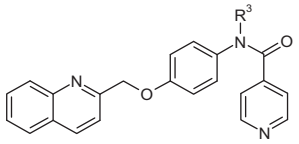
Compound	PDE10A IC_{50}[a] (nM)
1, papaverine	210
2, PQ10	64
3, MP10	2.6
4	32
8	250

[a] Values are means of three experiments with a standard deviation of ±30%.



Scheme 1. Synthesis of *N*-substituted anilides. Procedures: (a) R^1COCl, Et_3N, THF or R^1COOH, EDC·HCl, HOBt, DIPEA, DMF; (b) R^2CH_2Cl, K_2CO_3, CH_3CN; (c) R^3I, NaH, DMF.

Table 2
R^3 investigations



Compound	R^3	IC_{50}[a] (nM)
7	H	33% Inh @ 2 μM
8	CH_3	250
9	C_2H_5	750
10	C_4H_9	660

[a] Values are means of two experiments with a standard deviation of ±30%.

Next, we investigated the SAR at the R^1 substituent while maintaining R^2 and R^3 constant as the 2-quinoline (R^2) and methyl (R^3). The results of which are shown in Table 3.

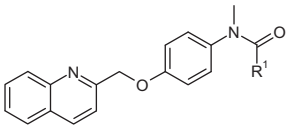
PDE10A affinity was diminished by a factor of **2** when the 4-pyridyl (**8**) was substituted with a phenyl (**11**) at the R1 position. More surprising was the significant affinity loss of the pyridyl-regioisomers **12** and **13**. Several analogues were prepared to investigate the limitations of the binding pocket: Compound **14**, a 6,5 bicyclic system, demonstrated the apparent relatively large volume available in the PDE10A binding pocket. Fusing the 6,5 system (**15**) yielded the first two-digit nanomolar inhibitor of PDE10A in this series. Inverting the system to a 5,6 bicyclic system yielded the most potent compounds **20** and **21**.

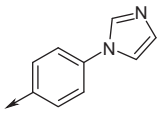
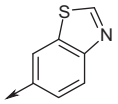
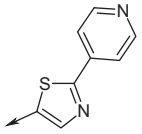
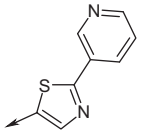
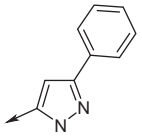
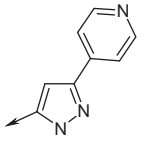
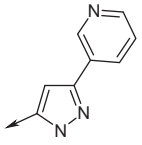
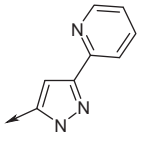
Investigations were now directed towards R^2. The parent compounds selected were **8** due to its high MPO score and compound **15** due to its high ligand efficiency and lack of requirement for protecting group chemistry. A total of 20 compounds were synthesised and a representative sample of those are shown in Table 4. All of the analogues synthesised were inferior in potency to the parent 2-quinolinyl substituted compounds.

Due to the conformational similarity of this compound series to the previously described clinical candidate MP-10, we decided to try to get a deeper understanding of the binding by studying X-ray crystal structures of complexes between MP-10 and the catalytic domain of PDE10A. In the PDE10A-MP10 complex, the pyrazole ring provides an appropriate angle for the molecule to extend into both the Q1 (pyridine binding) and Q2 (quinoline binding) pockets (Fig. 2).

A possible explanation for the reduction in potency of the primary amide **7** may be the that N–H anilides are almost exclusively in *trans* conformation, whereas *N*-methyl anilides are found almost exclusively in the *cis* conformation.[10] Thus, the *cis* conformation of *N*-methyl anilides may provide a conformational isostere for the pyrazole ring in MP-10 (Fig. 2).

Table 3
SAR investigations on diversity point R^1

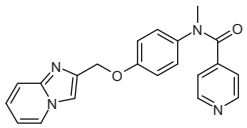
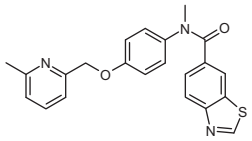
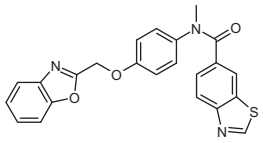
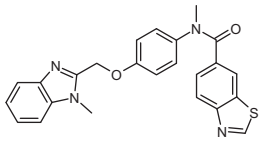


Compound	R1	PDE10A inhibition at 2 μM (%)	PDE10A IC_{50}[a] (nM)	MPO score	LEa
8		88	250	5.51	0.32
11		96	660	4.49	0.30
12		62	ND	5.51	ND
13		27	ND	5.51	ND
14		98	460	4.01	0.26
15		103	31	3.95	0.33
16		101	88	4.49	0.29
17		103	87	4.49	0.29
18		102	24	3.41	0.32
19		99	110	4.41	0.29
20		101	13	4.41	0.33
21		100	12	4.41	0.33

[a] ND is not determined.

In order to clarify the binding motif of the *N*-methyl anilides, compounds **8** and **19** were co-crystallized with PDE10A (Fig. 3). The X-ray structures confirmed the predicted binding of the quinoline moiety in the Q2 binding pocket similarly to MP-10. The *N*-methyl amide also provides the expected *cis* conformation, but unexpectedly the R^1 substituents of compound **8** and **19** are presented out of the Q1 binding pocket directed towards the divalent metals opposite of MP-10. This unexpected binding mode provides possible explanations of the SAR data. The higher potency of the 4-pyridyl (**8**) compared to the 2- and 3-pyridyl (**12** and **13**) may be due to the nitrogen in the 4-pyridyl being presented towards the water molecules encompassing the divalent metals. The X-ray studies also explains why bulky groups are tolerated as they extrude out of the binding pocket and why compounds

Table 4
SAR investigations on diversity point R^2

Compound	Structure	PDE10A inhibition at 2 μM (%)	PDE10A IC_{50} (nM)	MPO score	LE
22		88	1600	5.99	0.29
23		90	1600	5.03	0.28
24		98	920	4.55	0.28
25		104	61	4.31	0.32

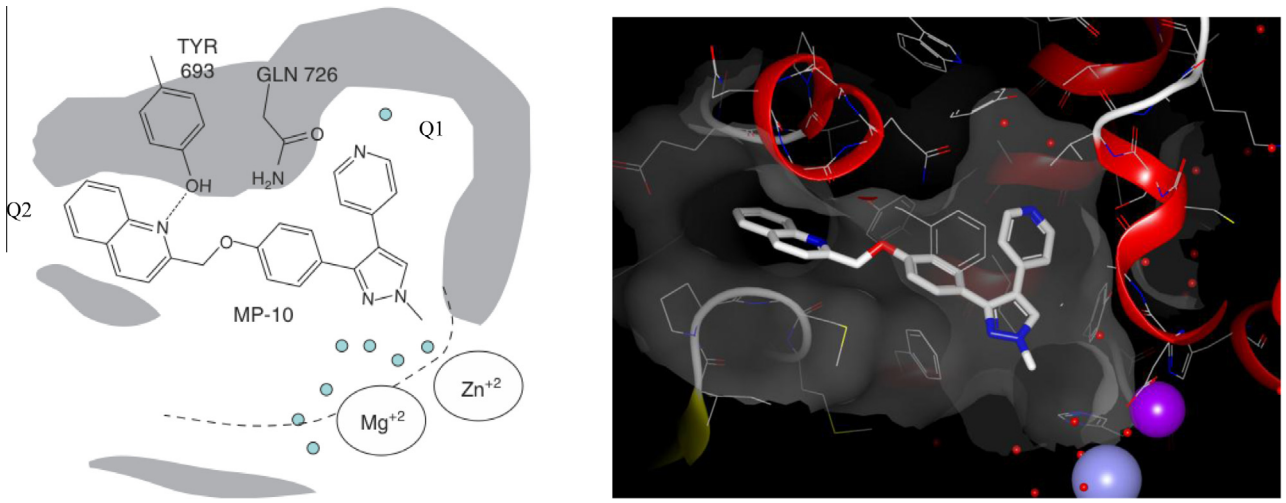


Figure 2. Left: illustration of the principle of the binding mode of MP-10. Right: X-ray crystal structure of MP-10 in complex with PDE10A determined by H. Lundbeck A/S (Not published, crystal structure almost identical to that of PDB 3HR1).[5d]

20 and **21** which present their pyridyl nitrogens towards the water enveloped divalent metals are highly potent PDE10A inhibitors.

We hypothesized that compounds **8** and **19** might be oriented differently than predicted by MP10 studies because the configuration of the amide bond enhanced the hydrogen bond between the *N*-methyl moieties to the N–H of Gln-726 forcing the R^1 substituent out of the binding pocket. Consequently, we decided to invert the amide bond to address the possible binding orientation of the corresponding *N*-methylbenzamides.

Synthesis strategies employed for substituted *N*-methylbenzamides are outlined in Scheme 2. The final compounds **26–32** were prepared from the intermediate 4-(quinolin-2-ylmethoxy)-benzoic acid[11] either directly via amide bond formation with *N*-methyl substituted amines or through amide bond formation with primary amines followed by N-methylation with methyl iodide.

The affinity and SAR of the relatively similar potencies between *N*-methylanilides (**8**, **11** and **15**) and the *N*-methylbenzamides (**26**, **29** and **32**) appeared to be similar (Table 5). However, an X-ray co-crystal structure of **32** bound to PDE10A (Fig. 4) revealed an MP10-like binding mode in this case. The *cis* conformation of the amide bond presents the R^1 substituent into the Q1 binding pocket and an overlay of the two co-crystal structures (MP10 and **32**) show the similarities in binding mode (Fig. 4). A similar binding mode was also observed for compound **32** (results not shown). Thus, inversion of the amide bond led to the intended binding mode, but surprisingly the different binding modes gave similar PDE10A affinity with only about twofold higher affinity of the 'correctly' binding *N*-methylanilides compared to the *N*-methylbenzamides.

Of the compounds made in development of this series, **15**, **21** and **32** were of particular interest in that they show high potency combined with a good MPO score or high ligand efficiency and good selectivity for PDE10A compared to other PDEs (Table 6).

A closer look at their respective metabolic stability in human liver microsomes indicates that as ligand efficiency increases, the corresponding human metabolic stability decreases. This decrease in human metabolic stability predicted from the decreasing MPO scores which reflects their increase in MW and lipophilicity (*c*Log *D*). Consequently, the observed decrease in human metabolic

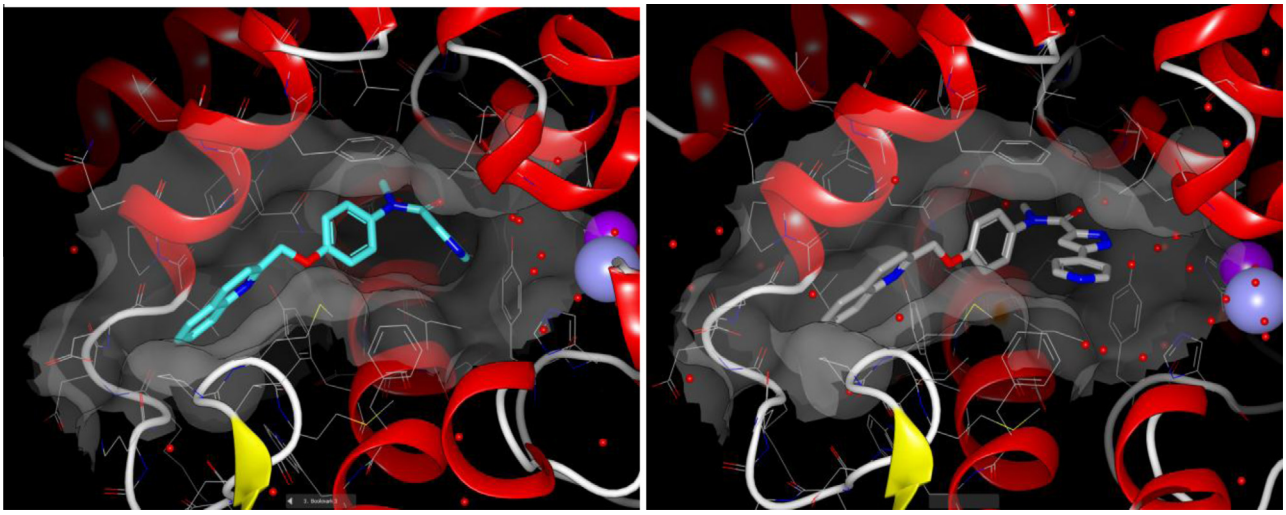
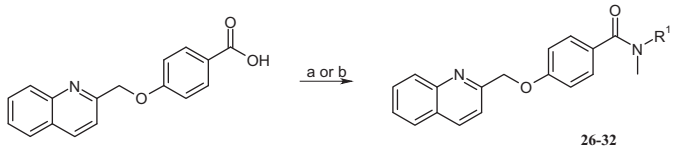


Figure 3. X-ray crystal structures of PDE10A in complex with **8** and **19** showing the binding mode. Divalent metals zinc and magnesium are shown in magenta and purple, respectively. Structure determined by H. Lundbeck A/S (Not published).



Scheme 2. Synthesis of N-substituted benzamides. Procedures: (a) R^1NHMe, HBTU, DIPEA or (b) R^1NH_2, HBTU, DIPEA then MeI, NaH, DMF.

stability and lack of potency (cf. MP10) of compound **15**, **21** and **32** meant the compounds did not meet the overall desired profile (HLM Cl, int <1.4 L/min and PDE10A IC_{50} <10 nM) which prevented the compounds from being further profiled in vivo (Table 7).

In summary, we have discovered substituted *N*-methylanilides and *N*-methylbenzamides as a novel class of PDE10A inhibitors. Employing structure–activity based drug design the initial potency was improved by 20-fold, the structure–activity observations were rationalized using X-ray crystal structure studies. Literature reports on the conformation of *N*-methylamides assisted in identifying a structural isostere for the pyrazole ring in MP-10. Although the initial aim of increasing potency was achieved, the resulting high microsomal intrinsic clearance of the compounds described and the inability to circumvent this issue resulted in none of the compounds being pursued further.

A. Experimental protocols

A.1. General

Unless otherwise stated, all solvents and reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. All reactions involving dry solvents or air-sensitive agents were performed under a nitrogen or argon atmosphere and glassware was dried prior to use. Solvents were dried according to standard procedures. Reactions were monitored by analytical thin-layer chromatography (TLC) analysis and analytical LC–MS. TLC was carried out using Merck silica gel 60 F_{254} aluminium sheets. The compounds were detected as single spots on TLC plates and visualised using UV light (254 nm) and different spraying reagents such as $KMnO_4$, ninhydrin, and bromocresol green, respectively. Flash chromatography was performed using either a CombiFlash Rf System (Teledyne Isco, Inc.) on Redi*Sep* columns or a Flashmaster II (Argonaut) on ISOLUTE Flash Si II columns. Eluent systems are given in volume/volume concentrations. ^{1}H NMR-spectra were recorded on a 500 MHz Bruker Avance AV500 instrument or on a 600 MHz Bruker Avance Ultrashield 600 plus instrument. The samples were prepared as $CDCl_3$ solutions using TMS/$CDCl_3$ as internal standards, or DMSO-d_6 solutions. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in Hertz (Hz). The following abbreviations are used: br = broad, s = singlet, d = doublet, dd = doublet of doublet, t = triplet, dt = doublet of triplet, tt = triplet of triplet, q = quartet, dq = doublet of quartet, m = multiplet.

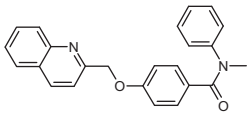
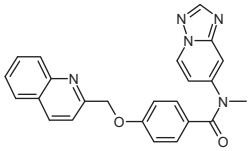
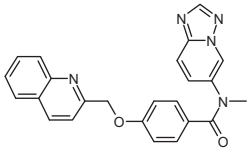
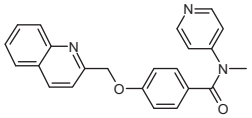
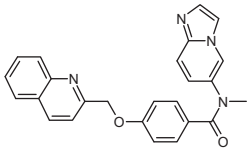
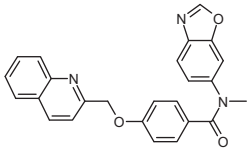
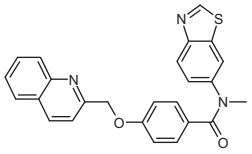
A.2. General procedure for the preparation of intermediates 5 exemplified by *N*-(4-Hydroxy-phenyl)-isonicotinamide

A solution of isonicotinoyl chloride (64 g, 0.46 mol) in dry THF (450 mL) was added dropwise into a solution of 4-aminophenol (50 g, 0.46 mol) and Et_3N (47 g, 0.46 mol) in dry THF (500 mL) cooled to 0 °C under an atmosphere of nitrogen. After the addition was complete, the mixture was stirred at rt for 8 h. The volatiles were removed under vacuum, and the residue was diluted with water (500 mL) and ether (500 mL). The organics was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum to give the title compound (66% yield) as a brown solid. ^{1}H NMR (DMSO-d_6 500 MHz TMS): δ 10.26 (s, 1H), 9.32 (s, 1H), 8.73 (dd, J = 4.4, 1.6 Hz, 2H), 7.81 (dd, J = 4.4, 1.6 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 6.73 (d, J = 8.8 Hz, 2H).

A.3. General procedure for the preparation of intermediates 6 exemplified by *N*-[4-(Quinolin-2-ylmethoxy)-phenyl]-isonicotinamide (7)

A slurry of *N*-(4-hydroxy-phenyl)-isonicotinamide (1.61 g, 0.75 mmol) and K_2CO_3 (3.10 g, 2.25 mmol) in dry CH_3CN (100 mL) was stirred at room temperature for 20 min, then 2-chloromethyl-quinoline (1.55 g, 0.75 mmol) was added. After addition was complete, the mixture was stirred at reflux overnight. After being cooled to room temperature, the reaction mixture was filtered, and the filtrate was concentrated under vacuum. The residue was crystallized from methanol to give the title compound as yellow solid (41% yield). ^{1}H NMR (DMSO-d_6 500 MHz TMS): δ 8.39 (d, J = 8.4 Hz, 1H), 8.01–7.96 (m, 2H), 7.92–7.89 (m, 2H), 7.78–7.74 (m, 1H), 7.67–7.64 (m, 3H), 7.61–7.57 (m, 1H), 7.53–7.45 (m, 3H), 7.05–7.01 (m, 2H), 5.33 (s, 2H). [M+H$^+$]: 356.2.

Table 5
SAR investigations on *N*-methylbenzamides

Compound	Structure	PDE10A inhibition at 2 μM (%)	PDE10A IC_{50} (nM)	MPO score	LE
26		94	950	4.31	0.30
27		100	400	5.34	0.28
28		101	240	5.34	0.29
29		101	140	5.56	0.34
30		105	130	4.65	0.30
31		105	93	4.63	0.31
32		109	16	3.94	0.34

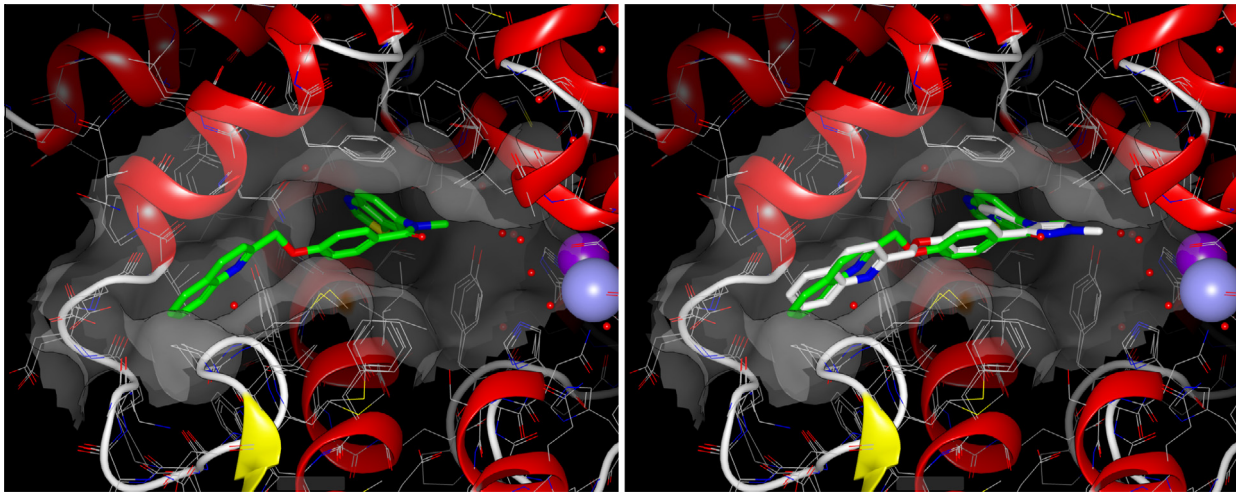


Figure 4. X-ray crystal structures of PDE10A in complex with 32 and an overlay of the two co-crystal structures of 32 (green) together with MP10 (white) showing very similar binding modes. Divalent metals zinc and magnesium are shown in magenta and purple, respectively. Structure determined by H. Lundbeck A/S (Not published).

Table 6
Selectivity of compounds **8**, **15**, **21** and **32** for PDE10A compared to other PDEs

	8	15	21	32
PDE10A	80	101	106	105
PDE2	14	1	12	15
PDE3A	16	ND	0	12
PDE4D	4	ND	0	13
PDE9	22	5	0	7

[a] ND is not determined. Results are given as% inhibition at 2 μM.

Table 7
Comparison of ligand efficiencies, MPO scores and metabolic stability (HLM Cl, int and RLM Cl, int) of compounds **8**, **15**, **21** and **32**

	8	15	21	32	MP10
PDE10A IC_{50} (nM)	250	31	12	16	2.6
LE	0.32	0.33	0.33	0.34	0.40
MW	369	425	435	425	392
*c*Log *D*	2.84	4.16	3.56	4.19	3.83
MPO	5.51	3.95	4.43	3.94	4.43
HLM Cl, int (L/min)	1.1	2.2	2.4	6.1	2.2
RLM Cl, int (L/min)	23	18	90	150	58

A.4. General procedure for the alkylation of intermediates (6) as exemplified by *N*-ethyl-*N*-(4-(quinolin-2-ylmethoxy)phenyl)isonicotinamide (8)

A mixture of *N*-[4-(quinolin-2-ylmethoxy)-phenyl]-isonicotinamide (100 mg, 0.29 mmol) and NaH (53 mg, 1.32 mmol) in dry DMF (3 mL) was stirred at room temperature for 15 min, then CH_3I (62 mg, 0.44 mmol) was added, the mixture was stirred an additional 2 h at rt, 2 drops of ice-water was added to quench the excess NaH. After evaporation, the residue was purified by preparative HPLC to give the tile compound as a yellow oil (26% yield) ^{1}H NMR (600 MHz, CD_3CN) δ 8.39 (s, 2H), 8.29 (d, J = 11.6 Hz, 1H), 8.00 (d, J = 11.6 Hz, 1H), 7.93 (d, J = 11.2 Hz, 1H), 7.76 (m, 1H), 7.59 (m, 2H), 7.08 (m, 4H), 6.92 (d, J = 9.2 Hz, 2H), 5.28 (s, 2H), 3.41 (s, 3H). [M+H$^+$]: 370.1.

A.5. *N*-Ethyl-*N*-(4-(quinolin-2-ylmethoxy)phenyl)isonicotinamide (9)

Prepared as described for compound **8** exchanging CH_3I for C_2H_5I to yield the title compound as a yellow oil (14% yield). ^{1}H NMR: (600 MHz, DMSO-d_6) δ 8.53–8.52 (m, 2H), 8.42–8.40 (m, 1H), 8.03–7.99 (m, 2H), 7.80–7.78 (m, 1H), 7.68–7.61 (m, 2H), 7.21–7.18 (m, 2H), 6.94–6.89 (m, 2H), 6.68–6.60 (m, 2H), 5.27 (s, 1H), 4.39–4.30 (m, 2H), 1.39–1.33 (m, 3H). [M+H$^+$]: 384.1.

A.6. *N*-Butyl-*N*-(4-(quinolin-2-ylmethoxy)phenyl)isonicotinamide (10)

Prepared as described for compound **8** exchanging CH_3I for n-C_4H_9I to yield the title compound as a yellow oil (12% yield). ^{1}H NMR (500 MHz, methanol-d_4): δ 8.80 (d, J = 8.4 Hz, 1H), 8.62 (d, J = 5.6 Hz, 2H), 8.21–8.16 (m, 2H), 8.01 (t, J = 7.6 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.75 (d, J = 6.4 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 5.49 (s, 2H), 3.94 (t, J = 7.2 Hz, 2H), 1.48–1.35 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H). [M+H$^+$]: 412.2.

A.7. *N*-Methyl-*N*-(4-(quinolin-2-yloxy)phenyl)benzamide (11)

Prepared as described for compound **8** exchanging *N*-(4-hydroxy-phenyl)-isonicotinamide for *N*-(4-hydroxy-phenyl)-benzamide to yield the title compound as a yellow oil (14% yield). ^{1}H NMR: (600 MHz, $CDCl_3$) δ 8.21–8.17 (m, 1H), 8.10–8.02 (m, 1H), 7.87–7.80 (m, 1H), 7.79–7.70 (m, 1H), 7.63–7.59 (m, 1H), 7.59–7.51 (m, 1H), 7.45-6.80 (m, 10H), 5.30 (s, 2H), 3.46 (s, 3H). [M+H$^+$]: 369.1.

A.8. *N*-Methyl-*N*-(4-(quinolin-2-yloxy)phenyl)nicotinamide (12)

Prepared as described for compound **8** exchanging *N*-(4-hydroxy-phenyl)-isonicotinamide for *N*-(4-hydroxy-phenyl)-nicotinamide to yield the title compound as a yellow oil (22% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.50 (s, 1H), 8.45–8.40 (m, 1H), 8.20–8.18 (m, 1H), 8.10–8.05 (m, 1H), 7.82–7.80 (m, 1H), 7.77–7.70 (m, 1H), 7.61–7.52 (m, 2H), 7.19-6.80 (m, 5H), 5.40 (s, 2H), 3.46 (s, 3H). [M+H$^+$]: 370.1.

A.9. *N*-Methyl-*N*-(4-(quinolin-2-yloxy)phenyl)picolinamide (13)

Prepared as described for compound **8** exchanging *N*-(4-hydroxy-phenyl)-isonicotinamide for *N*-(4-(quinolin-2-yloxy) phenyl)picolinamide to yield the title compound as a yellow oil (12% yield).

^{1}H NMR (500 MHz, methanol-d_4): δ 8.96 (d, J = 8.8 Hz, 1H), 9.38 (d, J = 7.2 Hz, 1H), 8.26 (t, J = 8.8 Hz, 2H), 8.09 (t, J = 7.6 Hz, 1H), 7.99 (t, J = 8.4 Hz, 1H), 7.89 (t, J = 7.6 Hz, 1H), 7.79 (t, J = 7.6 Hz, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.36 (t, J = 5.6 Hz, 1H), 7.17 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 5.56 (s, 2H), 3.47 (s, 3H). [M+H$^+$]: 370.1.

A.10. Benzothiazole-6-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide (14)

Benzothiazole-6-carboxylic acid (0.0717 g, 0.582 mmol) and 1-hydroxybenzotriazole (118 mg, 0.874 mmol) were dissolved in *N*,*N*-dimethylformamide (8 mL, 100 mmol). *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (0.168 g, 0.874 mmol) was added and the reaction was stirred at rt for 20 min. Methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amine (0.153 g, 0.582 mmol) was added followed by triethylamine (0.244 mL, 1.75 mmol). The reaction was stirred at room temperature for 20 h. H_2O (20 mL) was added to the reaction and the mixture was extracted with ethyl acetate (40 mL × 3). The combined organic phases were washed with satd aq $NaHCO_3$ (40 mL), dried with magnesium sulfate, filtered and evaporated. The crude product was purified using column chromatography. The product fractions were combined and evaporated and the residue crystallised from ethyl acetate/heptane to yield the title compound as an off white solid (20% yield). ^{1}H NMR: (600 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.17 (d, J = 8.7 Hz, 1H), 8.05 (d, J = 8.7 Hz, 1H), 8.01 (s, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.73 (dt, J = 1.4 Hz, J = 7.4 Hz, 1H), 7.59–7.53 (m, 2H), 7.35 (d, J = 8.2 Hz, 1H), 6.98 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 5.29 (s, 2H), 3.49 (s, 3H). [M+H$^+$]: 426.1.

A.11. 4-(1*H*-Imidazol-1-yl)-*N*-methyl-*N*-(4-(quinolin-2-ylmethoxy)phenyl)benzamide (15)

This compound was synthesized according to compound **14** but employing 4-(1*H*-imidazol-1-yl)benzoic acid instead of benzothiazole-6-carboxylic acid to yield the title compound as an off white solid (27% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.20–8.12 (m, 1H), 8.10–8.00 (m, 1H), 7.87–7.77 (m, 2H), 7.77–7.70 (m, 1H), 7.66–7.59 (m, 1H), 7.59–7.50 (m, 1H), 7.49-6.80 (m, 10H), 5.31 (s, 2H), 3.47 (s, 3H). [M+H$^+$]: 435.1.

A.12. *N*-Methyl-4-(pyridin-4-yl)-*N*-(4-(quinolin-2-yloxy)phenyl)thiazole-2-carboxamide (16)

This compound was synthesized according to compound **14** but employing 4-(pyridin-4-yl)thiazole-2-carboxylic acid instead of

benzothiazole-6-carboxylic acid to yield the title compound as an off white solid (60% yield). ^{1}H NMR: (500 MHz, DMSO-d_6) δ 8.69–8.60 (m, 2H), 8.34–8.27 (m, 1H), 8.02–7.95 (m, 3H), 7.82–7.74 (m, 1H), 7.67–7.52 (m, 4H), 7.21–7.15 (m, 2H), 7.05-6.99 (m, 2H), 5.43 (s, 2H), 3.47 (s, 3H). ([M+H$^+$]: 453.3).

A.13. *N*-Methyl-4-(pyridin-3-yl)-*N*-(4-(quinolin-2-yloxy)phenyl)thiazole-2-carboxamide (17)

This compound was synthesized according to compound **14** but employing 4-(pyridin-3-yl)thiazole-2-carboxylic acid instead of benzothiazole-6-carboxylic acid to yield the title compound as an off white solid (51% yield). ^{1}H NMR: (500 MHz, DMSO-d_6) δ 8.88–8.73 (br s, 1H), 8.68–8.59 (m, 1H), 8.36–8.26 (m, 1H), 8.04–7.93 (m, 4H), 7.80–7.75 (m, 1H), 7.49–7.45 (m, 1H), 7.20–7.15 (m, 2H), 7.04-6.97 (m, 2H), 5.33 (s, 2H), 3.47 (s, 3H). [M+H$^+$]: 453.2.

A.14. *N*-Methyl-5-phenyl-*N*-(4-(quinolin-2-yloxy)phenyl)-1*H*-pyrazole-3-carboxamide (18)

This compound was synthesized according to compound **14** but employing 5-phenyl-2*H*-pyrazole-3-carboxylic acid instead of benzothiazole-6-carboxylic acid to yield the title compound as an off white solid (50% yield). ^{1}H NMR: (500 MHz, $CDCl_3$) δ 11.16 (s, 1H), 8.15 (d, J = 8.2 Hz, 1H), 8.09 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.75 (dt, J = 7.5 Hz, J = 1.4 Hz, 1H), 7.67 (d, J = 8.9 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.52 (d, J = 7.5 Hz, 2H), 7.34 (t, J = 7.5 Hz, 2H), 7.31–7.26 (m, 1H), 7.21 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 8.8 Hz, 2H), 5.46 (s, 2H), 5.26 (br s, 1H), 3.43 (s, 3H). [M+H$^+$]: 434.9.

A.15. *N*-Methyl-5-(pyridin-4-yl)-*N*-(4-(quinolin-2-yloxy)phenyl)-1*H*-pyrazole-3-carboxamide (19)

This compound was synthesized according to compound **14** but employing 5-pyridin-4-yl-2*H*-pyrazole-3-carboxylic acid instead of benzothiazole-6-carboxylic acid to yield the title compound as an off white solid (52% yield). ^{1}H NMR: (500 MHz, $CDCl_3$) δ 11.80–11.50 (br s, 1H), 8.62–8.55 (m, 2H), 8.27–8.19 (m, 1H), 8.15–8.08 (m, 1H), 7.90–7.83 (m, 1H), 7.83–7.74 (m, 1H), 7.74–7.68 (m, 1H), 7.63–7.55 (m, 1H), 7.97–7.88 (m, 2H), 7.30–7.12 (m, 5H), 5.49 (s, 2H), 5.30 (s, 1H), 3.46 (s, 3H). [M+H$^+$]: 436.3.

A.16. *N*-Methyl-5-(pyridin-3-yl)-*N*-(4-(quinolin-2-yloxy)phenyl)-1*H*-pyrazole-3-carboxamide (20)

This compound was synthesized according to compound **14** but employing 5-pyridin-3-yl-2*H*-pyrazole-3-carboxylic acid instead of benzothiazole-6-carboxylic acid to yield the title compound as an off white solid (39% yield). ^{1}H NMR: (500 MHz, $CDCl_3$) δ 11.78 (s, 1H), 8.68 (s, 1H), 8.53 (dd, J = 4.8 Hz, J = 1.4 Hz, 1H), 8.27 (d, J = 8.2 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H), 7.94 (d, J = 7.9 Hz, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.74 (t, J = 7.4 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.55 (t, J = 7.4 Hz, 1H), 7.27 (dd, J = 8.1 Hz, J = 5.0 Hz, 1H), 7.21 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 8.8 Hz, 2H), 5.47 (s, 2H), 5.23 (br s, 1H), 3.44 (s, 3H). [M+H$^+$]: 436.2.

A.17. *N*-Methyl-5-(pyridin-2-yl)-*N*-(4-(quinolin-2-yloxy)phenyl)-1*H*-pyrazole-3-carboxamide (21)

This compound was synthesized according to compound **14** but employing 5-pyridin-2-yl-2*H*-pyrazole-3-carboxylic acid instead of benzothiazole-6-carboxylic acid to yield the title compound as an off white solid (39% yield). ^{1}H NMR: (500 MHz, $CDCl_3$) δ 11.58 (s, 1H), 8.54 (s, 1H), 8.15 (d, J = 8.2 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.71–7.63 (m, 3H), 7.55 (t, J = 7.7 Hz, 1H), 7.24–7.7.03 (m, 5H), 5.76 (br s, 1H), 5.42 (s, 2H), 3.44 (s, 3H). [M+H$^+$]: 436.2.

A.18. *N*-(4-(Imidazo[1,2-*a*]pyridin-2-yloxy)phenyl)-*N*-methylisonicotinamide (22)

Intermediate *N*-[4-(imidazo[1,2-*a*]pyridin-2-ylmethoxy)-phenyl]-isonicotinamide was synthesized according to compound **7** but employing 2-chloromethyl-imidazo[1,2-*a*]pyridine instead of 2-chloromethyl-quinoline. The title compound was prepared as described for compound **8** exchanging *N*-(4-hydroxy-phenyl)-isonicotinamide for *N*-[4-(imidazo[1,2-a]pyridin-2-ylmethoxy)-phenyl]-isonicotinamide to yield **22** as a yellow oil (26% yield). ^{1}H NMR (400 MHz, methanol-d_4): δ 8.79 (d, J = 6.8 Hz, 1H), 8.69 (d, J = 5.6 Hz, 2H), 8.30 (s, 1H), 8.00–7.96 (m, 2H), 7.92 (d, J = 8.8 Hz, 2H), 7.50–7.46 (m, 1H), 7.26–7.23 (t, 2H), 7.04–7.01 (t, 2H), 5.35 (s, 2H), 3.48 (s, 3H). [M+H$^+$]: 359.1.

A.19. Intermediate *N*-(4-hydroxyphenyl)-*N*-methylbenzo[*d*]thiazole-6-carboxamide

Benzothiazole-6-carboxylic acid (6.00 g, 33.5 mmol) and 1-hydroxybenzotriazole (6.79 g, 50.2 mmol) were dissolved in *N*,*N*-dimethylformamide (500 mL, 6000 mmol). Then *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (9.63 g, 50.2 mmol) was added and the reaction was stirred at room temperature for 20 min. 4-(Methylamino)phenol sulphate (5.76 g, 16.7 mmol) was added followed by triethylamine (14.0 mL, 1.00E2 mmol). The reaction was stirred at room temperature for 5 days. The reaction mixture was evaporated and the residue was suspended in H_2O (300 mL) and extracted with ethyl acetate (400 mL × 3). The combined organic phases were washed with sat. aq. $NaHCO_3$ (300 mL), dried with magnesium sulfate, filtered and evaporated. The crude product was purified using Combiflash (Silica, Column Size 220 g, Eluent: heptane:ethyl acetate). Fractions containing the product were combined and evaporated to yield the intermediate *N*-(4-hydroxyphenyl)-*N*-methylbenzo[*d*]thiazole-6-carboxamide (26%) as light brown crystals. ^{1}H NMR: (600 MHz, DMSO) δ 9.50 (s, 1H), 9.42 (s, 1H), 8.13 (br s, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.35 (br s, 1H), 7.00 (d, J = 8.2 Hz, 2H), 6.60 (d, J = 8.6 Hz, 2H), 3.34 (s, 3H). [M+H$^+$]: 284.9.

A.20. *N*-Methyl-*N*-(4-((6-methylpyridin-2-yl)methoxy)phenyl)isonicotinamide (23)

N-(4-Hydroxyphenyl)-*N*-methylbenzo[*d*]thiazole-6-carboxamide (200 mg, 0.77 mmol), 2-(chloromethyl)-6-methylpyridine (98.23 mg, 0.77 mmol), cesium carbonate (460 mg, 1.4 mmol) and potassium iodide (230 mg, 1.4 mmol) were stirred in acetone (30 mL) and heated to reflux for 21 h. The cooled reaction was mixed with 100 mL water and extracted with EtOAc (3 × 75 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and purified by flash chromatography (gradient, heptane to EtOAc), yielding the product as a white solid (40%).

^{1}H NMR: (500 MHz, DMSO-d_6) δ 9.41 (s, 1H), 8.14 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.66 (t, J = 7.7 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.22–7.17 (m, 1H), 7.14 (d, J = 8.5, 1H), 6.88 (d, J = 8.5 Hz, 1H), 5.02 (s, 2H), 3.36 (s, 3H), 2.44 (s, 3H). [M+H$^+$]: 390.1.

A.21. *N*-(4-(Benzo[d]oxazol-2-ylmethoxy)phenyl)-*N*-methylisonicotinamide (24)

This compound was synthesized according to compound **23** but employing 2-(chloromethyl)benzo[*d*]oxazole instead of 2-(chloromethyl)-6-methylpyridine to yield the title compound as an off

white solid (90% yield). ^{1}H NMR: (500 MHz, DMSO-d_6) δ 9.40 (s, 1H), 8.13 (s, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.74 (m, 2H), 7.40 (m, 3H), 7.17 (d, J = 8.6, 2H), 6.96 (d, J = 8.6, 2H), 5.38 (s, 2H), 3.36 (s, 3H). [M+H$^+$]: 416.1.

A.22. *N*-Methyl-*N*-(4-((1-methyl-1*H*-benzo[*d*]imidazol-2-yl)methoxy)phenyl)isonicotinamide (25)

This compound was synthesized according to compound **23** but employing 2-(chloromethyl)-1-methyl-1*H*-benzo[*d*]imidazole instead of 2-(chloromethyl)-6-methylpyridine to yield the title compound as a white solid (96%). ^{1}H NMR: (500 MHz, DMSO-d_6) δ 9.41 (s, 1H), 8.15 (s, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.1, 1H), 7.29 (t, J = 7.6, 1H), 7.22 (t, J = 7.6 Hz 1H), 7.17 (d, J = 8.5 Hz, 2H), 6.99 (d, J = 8.5 Hz, 2H), 5.33 (s, 2H), 3.79 (s, 3H), 3.36 (s, 3H). [M+H$^+$]: 429.1.

A.23. *N*-Methyl-*N*-phenyl-4-(quinolin-2-ylmethoxy)benzamide (26)

HBTU (147 mg, 0.39 mmol) and DIPEA (0.13 g, 1.0 mmol) were added to a solution of 4-(quinolin-2-ylmethoxy)benzoic acid (100 mg, 0.35 mmol) in DMF (5 mL), and the mixture was stirred at room temperature for 30 min *N*-methylaniline (38 mg, 0.35 mmol) was added, and the resulting mixture was stirred at room temperature for 12 h. Water (15 mL) was added, the resultant mixture was extracted with EtOAc (15 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by preparative HPLC to afford the title compound as an off white solid (11% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25–8.21 (m, 1H), 8.06–8.13 (m, 1H), 7.96–7.84 (m, 1H), 7.76–7.58 (m, 3H), 7.29–7.23 (m, 4H), 7.17–7.15 (m, 1H), 7.06–7.04 (m, 2H), 6.81 (d, J = 9.2 Hz, 2H), 5.35 (s, 2H), 3.50 (s, 3H). [M+H$^+$]: 369.1.

A.24. *N*-([1,2,4]Triazolo[1,5-*a*]pyridin-7-yl)-*N*-methyl-4-(quinolin-2-ylmethoxy)benzamide (27)

This compound was synthesized according to compound **26** but employing *N*-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-7-amine instead of *N*-methylaniline to yield the title compound as an off white solid (5% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (d, J = 7.2 Hz, 1 H), 8.23 (s, 1 H), 8.10 (d, J = 8.4 Hz, 1 H), 7.98 (d, J = 8.4 Hz, 1 H), 7.75 (d, J = 8.0 Hz, 1 H), 7.67 (t, J = 8.4 Hz, 1 H), 7.52–7.49 (m, 2 H), 7.35–7.29 (m, 3 H), 6.81 (d, J = 8.8 Hz, 1 H), 6.66–6.61 (m, 1 H), 5.27 (s, 2 H), 3.49 (s, 3 H). [M+H$^+$]: 410.0.

A.25. *N*-([1,2,4]Triazolo[1,5-*a*]pyridin-6-yl)-*N*-methyl-4-(quinolin-2-ylmethoxy)benzamide (28)

The intermediate 4-(quinolin-2-ylmethoxy)-*N*-[1,2,4]triazolo[1,5-a]pyridin-7-yl-benzamide was synthesized according to compound **26** but employing [1,2,4]triazolo[1,5-*a*]pyridin-7-ylamine instead of *N*-methylaniline. To a solution of 4-(quinolin-2-ylmethoxy)-*N*-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl-benzamide (0.1 g, 0.25 mmol) in dry DMF (2 mL) was added NaH (12 mg, 0.5 mmol) at 0 °C, after 15 min, 36 mg of CH_3I was added into, the reaction mixture was stirred at room temperature for 30 min. 10 mL of water was poured into the mixture, and extacted with EtOAc, the combined organic layer was concentrated and the residue was purified by preparative HPLC to give yield the title compound (yield: 26%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.35–8.32 (m, 2H), 8.17–8.15 (m, 1H), 8.05–8.03 (m, 1H), 7.83–7.81 (m, 1H), 7.75–7.71 (m, 1H), 7.68–7.66 (m, 1H), 7.56–7.54 (m, 2H), 7.37–7.32 (m, 3H), 6.86–8.84 (m, 2H), 5.31 (s, 2H), 3.51 (s, 3H). [M+H$^+$]: 410.0.

A.26. *N*-Methyl-*N*-(pyridin-4-yl)-4-(quinolin-2-ylmethoxy)benzamide (29)

This compound was synthesized according to compound **26** but employing *N*-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-7-amine instead of *N*-methylaniline to yield the title compound (7% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (s, 2H), 8.18 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.74 (m, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.56 (m, 1H), 7.31 (m, 2H), 6.93 (d, J = 5.2 Hz, 2H), 6.88 (m, 2H), 5.35 (s, 2H), 3.50 (s, 3H). [M+H$^+$]: 370.1.

A.27. *N*-(Imidazo[1,2-*a*]pyridin-6-yl)-*N*-methyl-4-(quinolin-2-ylmethoxy)benzamide (30)

The intermediate *N*-imidazo[1,2-*a*]pyridin-6-yl-4-(quinolin-2-ylmethoxy)-benzamide was synthesized according to compound **26** but employing imidazo[1,2-*a*]pyridin-6-ylamine instead of *N*-methylaniline. Methylation of the intermediate *N*-imidazo[1,2-*a*]pyridin-6-yl-4-(quinolin-2-ylmethoxy)-benzamide was performed as described for compound **28** to yield the title compound as a yellow oil (9% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17–8.14 (m, 1H), 8.06–8.04 (m, 1H), 7.83–7.75 (m, 2H), 7.73–7.71 (m, 1H), 7.62–7.57 (m, 4H), 7.45 (s, 1H), 7.34–7.32 (m, 2H), 7.07–7.04 (m, 1H), 6.85–6.83 (m, 2H), 5.31 (s, 2H), 3.47 (s, 3H). [M+H$^+$]: 409.1.

A.28. *N*-(Benzo[*d*]oxazol-6-yl)-*N*-methyl-4-(quinolin-2-ylmethoxy)benzamide (31)

The intermediate *N*-benzooxazol-6-yl-4-(quinolin-2-ylmethoxy)-benzamide was synthesized according to compound **26** but employing benzooxazol-6-ylamine instead of *N*-methylaniline. Methylation of the intermediate *N*-benzooxazol-6-yl-4-(quinolin-2-ylmethoxy)-benzamide was performed as described for compound **28** to yield the title compound as a yellow oil (20% yield). ^{1}H NMR (500 MHz, CD_3CN): δ 8.31–8.29 (m, 2H), 7.99–7.97 (m, 1H), 7.92–7.91 (m, 1H), 7.78–7.74 (m, 1H), 7.62–7.56 (m, 3H), 7.47–7.46 (m, 1H), 7.26–7.19 (m, 3H), 6.84–6.82 (m, 2H), 5.26 (s, 2H), 3.42 (s, 3H). [M+H$^+$]: 410.1.

A.29. *N*-(Benzo[*d*]thiazol-6-yl)-*N*-methyl-4-(quinolin-2-ylmethoxy)benzamide (32)

The intermediate *N*-benzothiazol-6-yl-4-(quinolin-2-ylmethoxy)-benzamide was synthesized according to compound **26** but employing benzothiazol-6-ylamine instead of *N*-methylaniline. Methylation of the intermediate *N*-benzothiazol-6-yl-4-(quinolin-2-ylmethoxy)-benzamide was performed as described for compound **28** to yield the title compound as a yellow oil (69% yield). ^{1}H NMR (500 MHz, methanol-d_4): δ 9.21 (s, 1H), 8.73–8.70 (m, 1H), 8.14–8.10 (2H), 7.98–7.93 (m, 2H), 7.82–7.76 (m, 3H), 7.32–7.29 (m, 3 H), 6.92–6.89 (m, 2H), 5.43 (s, 2H), 3.52 (s, 3H). [M+H$^+$]: 426.0.

References and notes

1. Beavo, J. A.; Brunton, L. L. *Nat. Rev. Mol. Cell Biol.* **2002**, *3*, 710.
2. (a) Hebb, A.; Robertson, H. A. *Curr. Opin. Pharmacol.* **2007**, *7*, 86; (b) Menniti, F. S.; Faraci, W. S.; Schmidt, C. J. *Nat. Rev. Drug Disc.* **2006**, *5*, 660.
3. Conti, M.; Beavo, J. *Annu. Rev. Biochem.* **2007**, *76*, 481.
4. (a) Menniti, F. S.; Chappie, T. A.; Humphrey, J. M.; Schmidt, H. C. *Curr. Opin. Invest. Drugs* **2007**, *8*, 54; (b) Siuciak, J. A. *CNS Drugs* **2008**, *22*, 983; (c) Halene, T. B.; Siegel, Steven J. *Drug Discovery Today* **2007**, *12*, 870; (d) Siuciak, J. A.; Chapin, D. S.; Harms, J. F.; Lebel, L. A.; McCarthy, S. A.; Chambers, L.; Shrikhande, A.; Wong, S.; Menniti, F. S.; Schmidt, C. J. *Neuropharmacology* **2006**, *51*, 386; (e) Brandon, N. J.; Rotella, D. P. *Annu. Rep. Med. Chem.* **2007**, *42*, 3.
5. (a) Kehler, J.; Ritzén, A.; Rodriguez, G. D. *Expert Opin. Ther. Pat.* **2007**, *17*, 147; (b) Chappie, T. A.; Humphrey, J. M.; Allen, M. P., et al *J. Med. Chem.* **2007**, *50*, 182; (c) Chappie, T.; Humphrey, J.; Menniti, F.; Schmidt, C. *Curr. Opin. Drug Disc. Dev.*

2009, *12*, 458; (d) Kehler, J.; Kilburn, J. P. *Expert Opin. Ther. Patents* **2009**, *19*, 1715.
6. Verhoest, P. T.; Chapin, D. S.; Corman, M.; Fonseca, K.; Harms, J. F.; Hou, X.; Marr, E. S.; Menniti, F. S.; Nelson, F.; O'Connor, R.; Pandit, J.; Proulx-LaFrance, C.; Schmidt, A. W.; Schmidt, C. J.; Suiciak, J. A.; Liras, S. *J. Med. Chem.* **2009**, *52*, 5188.
7. Hoefgen, N.; Stange, H.; Schindler, R.; Lankau, H.-J.; Grunwald, C.; Langen, B.; Egerland, U.; Tremmel, P.; Pangalos, M. N.; Marquis, K. L.; Hage, T.; Harrison, B. L.; Malamas, M. S.; Brandon, N. J.; Kronbach, T. *J. Med. Chem.* **2010**, *53*, 4399.
8. Kostowski, W.; Gajewska, S.; Bidzinski, A.; Hauptman, M. *Pharmacol., Biochem. Behav.* **1976**, *5*, 15.
9. Wager, T. T.; Hour, X. V. P. R.; Villalobos, A. *ACS Chem. Neurosci.* **2010**, *1*, 435.
10. (a) Krebs, F. C.; Larsen, M.; Jørgensen, M.; Jensen, P. R.; Bielecki, M.; Schaumburg, K. *J. Org. Chem.* **1998**, *63*, 9872; (b) Itai, A.; Toriumi, Y.; Saito, S.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1992**, *114*, 10649; (c) Azumaya, I.; Kagechika, H.; Yamaguchi, K.; Shudo, K. *Tetrahedron* **1995**, *51*, 5277; (d) Yamaguchi, K.; Matsumura, G.; Kagechika, H.; Azumaya, I.; Ito, Y.; Itai, A.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 5474; (e) Azumaya, I.; Yamaguchi, K.; Okamoto, I.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 9083; (f) Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1996**, *118*, 7529; (g) Kashino, S.; Matsusita, T.; Iwamoto, T.; Yamaguchi, K.; Haisa, M. *Acta Crystallogr.* **1986**, *C42*, 457; (h) Azumaya, I.; Yamaguchi, K.; Kagechika, H.; Saito, S.; Itai, A.; Shudo, K. *J. Pharm. Soc. Jpn.* **1994**, *114*, 414.
11. Verhoest, P. R.; Helal, C. J.; Hoover, D. J.; Humphrey, J. M. US2006/0154931 A1.