Available online at www.sciencedirect.com
ScienceDirect
European Journal of Medicinal Chemistry 43 (2008) 1444–1453
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Original article

Inhibition of PDGFR tyrosine kinase activity by a series of novel *N*-(3-(4-(pyridin-3-yl)-1*H*-imidazol-2-ylamino)phenyl) amides – A SAR study on the bioisosterism of pyrimidine and imidazole

Siavosh Mahboobi [a,*], Andreas Sellmer [a], Asma Eswayah [a], Sigurd Elz [a], Andrea Uecker [b], Frank-D. Böhmer [b]

[a] *Institute of Pharmacy, Faculty of Chemistry and Pharmacy, University of Regensburg, D-93040 Regensburg, Germany*
[b] *Institute of Molecular Cell Biology, Jena University Hospital, D-07747 Jena, Germany*

Received 19 June 2007; received in revised form 12 September 2007; accepted 13 September 2007
Available online 2 October 2007

This paper is dedicated to Professor Wolfgang Wiegrebe on the occasion of his 75th birthday.

Abstract

A series of *N*-(3-(4-(pyridin-3-yl)-1*H*-imidazol-2-ylamino)phenyl)amides were synthesized and tested for inhibition of PDGFR and FLT3 autophosphorylation. The novel *N*-(3-(4-(pyridin-3-yl)-1*H*-imidazol-2-ylamino)phenyl)amides, obtained by replacement of the pyrimidine system in Imatinib (**1**) with an imidazole ring, exhibit potent inhibitory activity on PDGFR, similar to the parent compound (IC_{50} (**9e**) = 0.2 μM; IC_{50} Imatinib (**1**) = 0.3 μM). Selectivity hereby seems to be conserved, as shown by the lack of activity on FLT3, a closely related class III receptor tyrosine kinase, which is not affected by the parent compound Imatinib.

Keywords: 1*H*-Imidazol-2-ylamine; Pyrimidine; Receptor tyrosine kinase; PDGFR; Bioisosterism

1. Introduction

Selective inhibition of protein kinases appears as an effective therapeutic approach for the treatment of certain types of human cancer [1]. Platelet-derived growth factor receptors (PDGFRs) have been implicated in a number of pathologies, especially in various cancers, and are therefore considered as promising drug targets (for review see Refs. [2,3]. The two types of PDGF receptors, PDGFRα and β, are members of the class III receptor tyrosine kinase (RTK) family, which also includes the receptors for the stem cell factor (c-KIT), for the colony stimulating factor 1 (CSF1R), and FLT3. PDGF receptors are expressed on several cell types, including fibroblasts, vascular smooth muscle cells, and pericytes, and are involved in wound healing and regulation of homeostasis of the connective tissue compartment [4]. A very well known and highly selective tyrosine kinase inhibitor is STI571 (Imatinib, **1**) (Fig. 1). Imatinib is active towards both isoforms of PDGFR [5,6] Moreover, Imatinib is highly active towards ABL/BCR-ABL [7] and c-KIT, and, based on this capacity, is successfully used in the therapy of chronic myeloid leukemia (CML), and gastrointestinal stroma tumors [8–10].

The pharmacophore for this compound, described in early reports from Zimmermann et al. [5], comprises the following features: (i) a *N*-phenylpyrimidin-2-amine (b-ring system) substituted in position 4 with a 3-pyridyl-substituent (a-ring system; part A). (ii) The phenylamino substituent is moreover

* Corresponding author. Tel.: +49 (0)941 943 4824; fax: +49 (0)941 943 1737.
E-mail address: siavosh.mahboobi@chemie.uni-regensburg.de (S. Mahboobi).

0223-5234/$ - see front matter © 2007 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2007.09.021

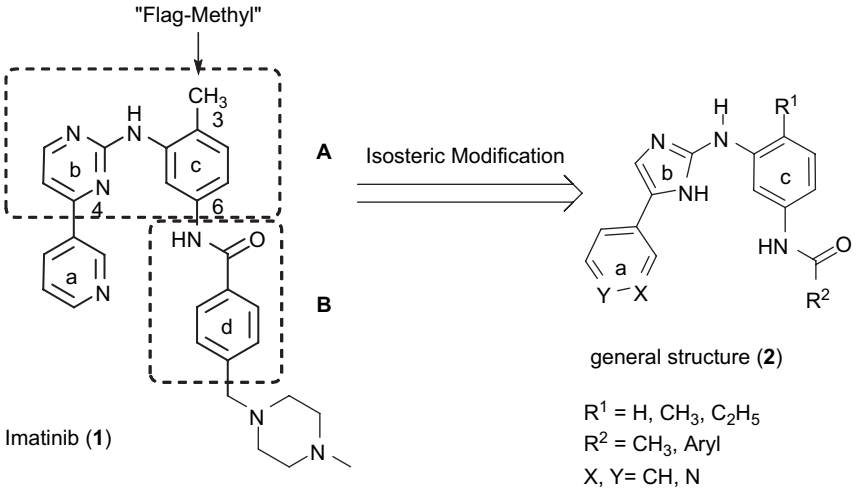


Fig. 1. Structure of Imatinib® (**1**) (left) and general structure (**2**) of the isosterically modified imidazolyl analogs investigated (right). The pharmacophore of Imatinib® responsible for PDGFR inhibitory activity is shown in bold. Without substitution of the Flag-Methyl group, compounds of the phenylaminopyrimidine class have also been shown to be potent inhibitors of PKC-subtypes α,δ and c-SRC.

modified as shown in Fig. 1 by substitution with methyl (or chlorine) in position 3 of the c-ring system and by substitution with a benzamide substructure in position 6. Hereby, the so called ''Flag-Methyl'' group has been shown to be responsible for enhancement of PDGFR inhibitor activity as well as selectivity. (iii) The benzamide substituent preferably bears a lipophilic substructure in *para* position (substructure part B).

However, to what extent are the described structural requirements essential for full inhibitory activity? To answer this question, we investigated several derivatives replacing the pyrimidine ring system by an imidazolyl system, a strategy that has obviously also been pursued by Ciufolini et al. in a similar manner, who recently patented aminoaryl substituted, five-membered heterocyclic compounds for the treatment of diseases and described their inhibitory activity towards wild type and mutated c-KIT [11].

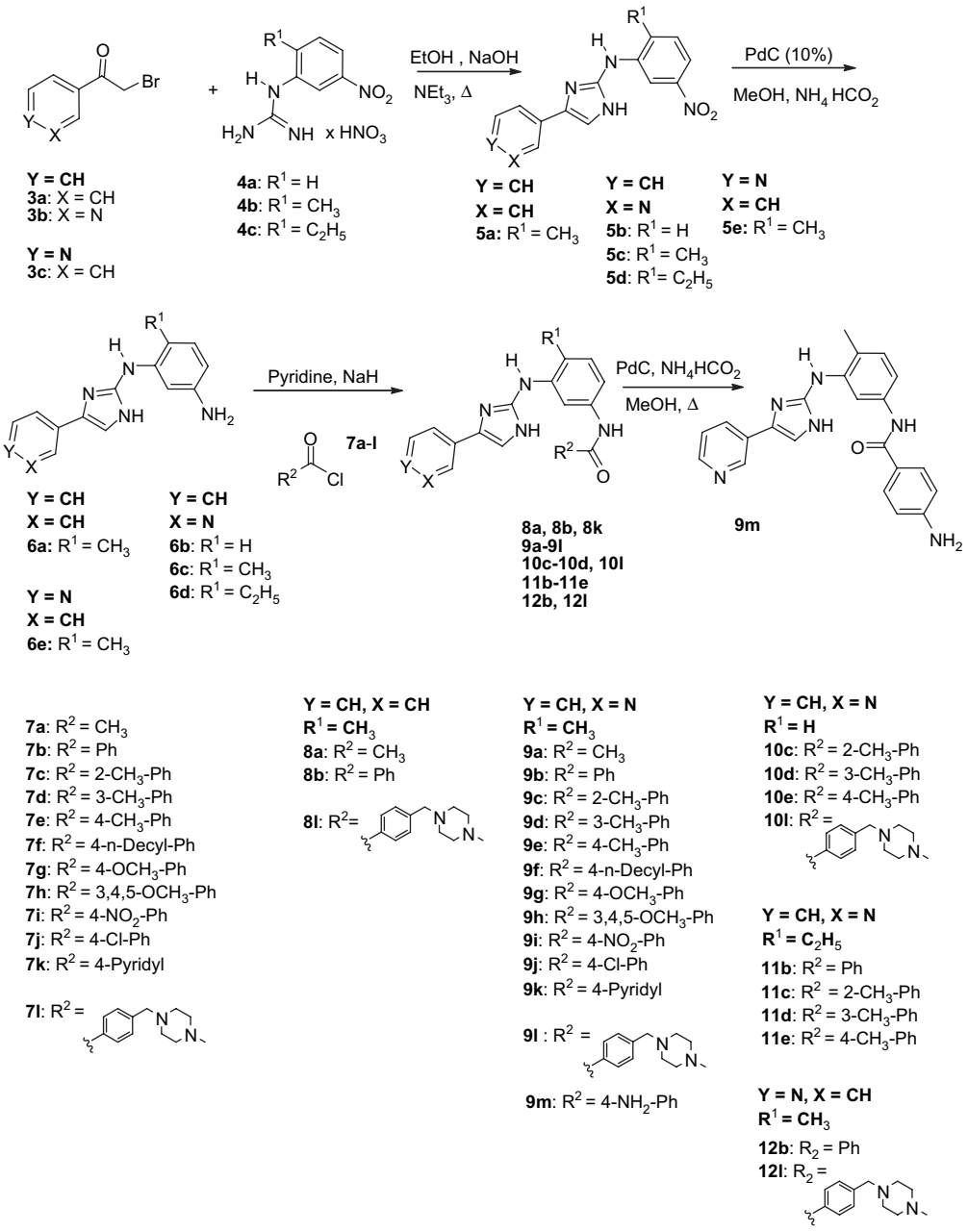
2. Chemistry

The first stage of our study comprised the synthesis of the imidazolyl isostere of the Imatinib® pharmacophore and a series of derivatives, where the 3-pyridyl ring was replaced by benzene and, with respect to the modified geometrical structure resulting from the exchange of a six-membered ring system by a five-membered ring system, by a 4-pyridyl substituent. Chemical modification was then performed by replacing the benzamide substructure in position 3 or modifying this substituent. Finally, also the influence of the ''Flag-Methyl'' group was investigated. The synthetic route (Scheme 1), which was simultaneously developed for the synthesis of the structurally closely related *N*-(3-(4-(pyridin-4-yl)-1*H*-imidazol-2-ylamino)phenyl)amides in a similar manner by Ciufolini et al. [11], is described in the following: ring closure of 2-bromo-1-phenylethanone (**3a**) or 2-bromo-1-(pyridinyl)ethanone hydrobromides **3b** [12] and **3c** [13] with suitably substituted 1-(3-nitrophenyl)guanidine nitrates **4a** [14], **4b** [15] or **4c** led to the desired *N*-(2-methyl-5-nitrophenyl)-4-phenyl-1*H*-imidazol-2-amine (**5a**), respectively, to the *N*-(3-nitrophenyl)-4-(pyridinyl)-1*H*-imidazol-2-amines **5b**–**5e**. Catalytic reduction with ammonium formate on PdC in methanolic solution led to 6-methyl-N^1-(4-phenyl-1*H*-imidazol-2-yl)benzene-1,3-diamine (**6a**) and N^1-(4-(pyridinyl)-1*H*-imidazol-2-yl)benzene-1,3-diamines **6b**–**6e**, which were transformed to the corresponding amides **8a**–**12** (Scheme 1) by reaction with carboxylic acid chlorides (**7a**–**7l**). In case of **9i**, the arylamide was additionally modified by reduction of the nitro group, affording the corresponding amino derivative **9m**.

3. Results and discussion

The five-membered ring system of imidazole exhibits an additional hydrogen bridge donor, and lacks one hydrogen bridge acceptor in comparison to pyrimidine. An exchange of donor and acceptor hereby is easily possible by tautomerism [16]. The heterocyclic imidazolyl analog moreover exhibits a modified molecular geometry, caused by the changed binding angles. Therefore, as already mentioned above, the 3-pyridyl ring was replaced by benzene and by a 4-pyridyl substituent, with respect to the modified geometrical structure resulting from the exchange of a six-membered ring system by a five-membered ring system, in addition. A summary of the biological data for inhibition of PDGFR by 2-arylaminoimidazolyl compounds modifying the pyridine and amide substituent is compiled in Table 1. To determine if the selectivity of the compounds was retained, activity on FLT3, a closely related member of the class III receptor tyrosine kinase (RTK) family, which is not affected by the parent compound Imatinib [17,18], was tested additionally.

As shown in Table 1, exchange of the pyrimidine to an imidazole system is well tolerated. In case of **9a**, even an enhancement in activity compared to the pyrimidine compound (**13**) can be observed (5.9 μM *vs.* 50 μM). As in the parent



Scheme 1. Synthesis of target compounds.

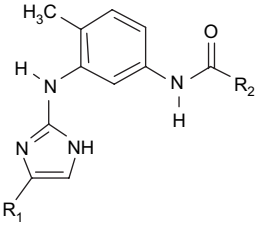
compound, the 3-pyridyl-substituted derivatives (**9a**, **9b**) exhibit most potent inhibitory activity, decreasing by replacement of the 3-pyridyl substituent by phenyl (**8b**), and even more significant by replacement by 4-pyridyl (**12b**).

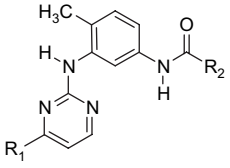
The amide substructure is essential for activity. All investigated compounds lacking this structural feature (compounds **5a**–**5e** and **6a**–**6e**, Scheme 1) neither inhibited PDGFR nor FLT3 up to concentrations of 10 μg/mL (data not shown). As reported for the pyrimidine series [5], the benzamides **8b** and **9b** are superior to their corresponding acetamides **8a** and **9a**. In contrast to the pyrimidine series, introduction of the 1-methyl-4-benzylpiperazine in the imidazolyl series is detrimental (**9l** *vs*. **9b**). None of the investigated compounds affected FLT3 up to concentrations of 10 μg/mL.

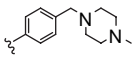
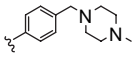
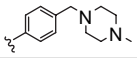
For the 3-pyridyl compounds exhibiting most potent inhibitory activity, we studied the influence of the substitution patterns of the benzamide substituent in this system in the following. The investigated compounds are compiled in Table 2. Again, none of these compounds affected FLT3 up to concentrations of 10 μg/mL.

In case of the pyrimidine series, substitution by a lipophilic substituent in *para* position of the benzamide substructure led to significant increase of potency [5]. In case of the imidazolyl compounds, however, *para*-substitution in the benzene ring by methyl (**9e**) or chlorine (**9j**) is tolerated, but affects activity only slightly, showing best inhibitory activity for the 4-methyl derivative **9e**. Introduction of more voluminous substituents, as demonstrated by the C10-chain of **9f** reduces activity as much

Table 1
Inhibition of PDGFR by 2-arylaminoimidazolyl compounds





R_1	R_2	Nr.	IC_{50} PDGFR [μM]	Nr.	IC_{50} PDGFR [μM]
Ph	CH_3	**8a**	>30		
3-Pyridyl	CH_3	**9a**	5.9 μM	**13**	50 [5]
Ph	Ph	**8b**	7.1		[a]
3-Pyridyl	Ph	**9b**	0.3	**14**	0.1–0.3 [5]
4-Pyridyl	Ph	**12b**	>10		[a]
Ph		**8l**	>10		[a]
3-Pyridyl		**9l**	>10	Imatinib (**1**)	0.3[b]
4-Pyridyl		**12l**	>10		

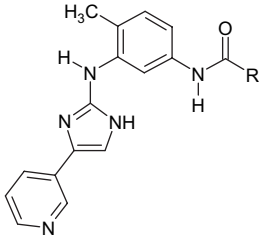
[a] No data from literature.
[b] Values for Imatinib as a reference compound in the used swiss 3T3 cell model.

as introduction of methoxy groups (**9g**, **9h**) or introduction of nitro (**9i**) or amino groups does (**9m**). The 4-pyridyl-substituent (**9k**) instead of a benzene system (**9b**) is tolerated much better.

In the following, the effect of the ''Flag-Methyl'' in the imidazolyl system was investigated, replacing this group by hydrogen or an ethyl substituent. With respect to the changed geometrical structure, chemical modification was also performed including different substitution patterns in the benzamide system (Table 3).

As demonstrated by the data shown in Table 3, highest inhibitory activity is observed within the series of compounds **9** and **10**, being substituted in *para* position by a methyl group. Comparing the data of **9c–9e** and **10c–10e**, no significant effect by introduction of the ''Flag-Methyl'' group can be observed, also **9e** exhibits similar activity as **10e**. In contrast, for the series **11b–11e** inhibitory activity is highest for the *meta*-substituted compound **11d**, exhibiting an IC_{50} value of 0.3 μM. Also in case of **10l**, as already seen for the series of compounds **9**, introduction of the 1-methylene-4-methylpiperazine-substructure is detrimental for activity.

Table 2
Inhibition of PDGFR by 2-arylaminoimidazolyl compounds by modification of the amide substituent



	Nr.	IC_{50} PDGFR [μM]
4-Ph	**9b**	**0.3**
4-CH_3-Ph	**9e**	**0.2**
4-*n*-Decyl-Ph	**9f**	>10
4-OCH_3-Ph	**9g**	>30
3,4,5-OCH_3-Ph	**9h**	>10
4-NO_2-Ph	**9i**	>30
4-Chlor-Ph	**9j**	**0.4**
4-Pyridyl	**9k**	1.8
4-NH_2	**9m**	>30

4. Conclusions

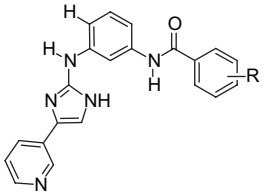
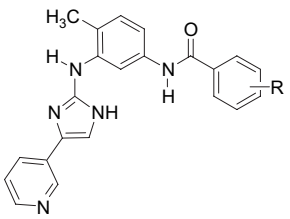
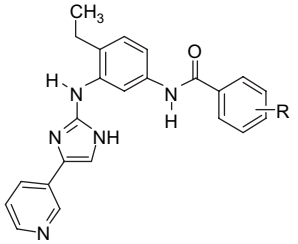
The novel *N*-(3-(4-(pyridin-3-yl)-1*H*-imidazol-2-ylamino)-phenyl)amides, obtained by replacement of the pyrimidine system in Imatinib (**1**) by an imidazole ring, exhibit potent inhibitory activity on PDGFR, similar to the parent compound (IC_{50} (**9e**) = 0.2 μM; IC_{50} Imatinib (**1**) = 0.3 μM). Selectivity hereby seems to be conserved, as shown by the lack of activity on FLT3, a closely related receptor tyrosine kinase, which is not affected by the parent compound Imatinib.

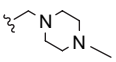
As in the parent pyrimidine series, the amide substructure is essential for activity as well as substitution of the b-ring by a 3-pyridyl substituent. Also, as observed for the parent compounds, benzamides in general are superior to acetamides, but in contrast to the pyrimidine series, introduction of a methyl group in position 3 of the c-ring system (Fig. 1) affects activity only slightly.

5. Experimental part

Inhibition of PDGF receptors and of FLT3 were assessed in Swiss 3T3 fibroblasts or in EOL-1 cells, respectively, exactly

Table 3
Inhibition of PDGFR by 2-arylaminoimidazolyl compounds – modification of the c-ring system and the benzamide substituent

R_1	Nr.	IC_{50} PDGFR [μM]	Nr.	IC_{50} PDGFR [μM]	Nr.	IC_{50} PDGFR [μM]
H			**9b**	0.3	**11b**	4.7
2-CH_3	**10c**	0.6	**9c**	0.6	**11c**	1.6
3-CH_3	**10d**	0.3	**9d**	2.2	**11d**	0.3
4-CH_3	**10e**	0.2	**9e**	0.2	**11e**	6.5
	**10l**	6.5	**9l**	>10		

as previously described [19]. All IC_{50} values were derived from duplicate or triplicate determinations, and were determined from a concentration curve comprising six concentrations using the program SigmaPlot (Systat Software Inc.) as described earlier [20]. The standard errors of the mean (SEM) are always in the range of ±50%.

6. Chemical procedures

6.1. General

NMR spectra were recorded with a Bruker Avance 300 MHz spectrometer at 300 K, using TMS as an internal standard. IR spectra (KBr or pure solid) were measured with a Bruker Tensor 27 spectrometer. Melting points were determined with a Büchi B-545. MS spectra were measured with a Finnigan MAT 95 (EI, 70 eV), or with a Finnigan Thermo Quest TSQ 7000 (ESI) (DCM/MeOH + 10 mmol/l NH_4Ac). All reactions were carried out under nitrogen atmosphere. Elemental analyses were performed by the Analytical Laboratory of the University of Regensburg.

6.2. Preparation of *4a-4c* – general procedure A

To a stirred suspension of the respective guanidinium nitrate **4a** [14], **4b** [15] or **4c** (23.4 mmol) in ethanol (300 mL), powdered KOH (23.4 mmol, 1.31 g) was added and the mixture heated to 80 °C, liberating the free base of guanidine *in situ*. A mixture of the respective 2-bromo-1-arylethanone (**3a–3c**) (23.4 mmol) and triethylamine (23.4 mmol) in 150 mL of ethanol was added within half an hour and the mixture stirred at 80 °C for 12 h. The solvent was removed under reduced pressure, diluted aqueous ammonia solution was added (100 mL) and the residue extracted with ethyl acetate (3 × 250 mL). The combined organic layers were dried (Na_2SO_4), the solvent removed under reduced pressure, and the product purified by column chromatography (SiO_2; CH_2Cl_2/MeOH 10:1; vol./vol.) and crystallisation from ethyl acetate.

6.2.1. N-(2-Methyl-5-nitrophenyl)-4-phenyl-1H-imidazol-2-amine (*5a*)

Yield: 3.84 g (55%), yellow crystals, mp: 186.8–187.1 °C. IR (KBr): ν (cm^{-1}) = 3405, 1652. ^1H NMR (DMSO-d_6): δ (ppm) = 2.26 (s, 3H), 5.61 (s, 2H, exchangeable), 7.11–7.19 (m, 1H, aromat.), 7.27–7.37 (m, 3H, aromat.), 7.66–7.75 (m, 3H, aromat.), 8.14 (d, 1H, J = 2.3 Hz, aromat.), 8.26 (dd, 1H, J = 2.3 Hz, J = 8.5 Hz,). EI-MS (70 eV) *m/z* (%): 294 (100) $[M]^{+\bullet}$, 264 (5), 248 (6). Anal. ($C_{16}H_{14}N_4O_2 \cdot 1/4H_2O$): C 64.31 H 4.89 N 18.75 Found: C 64.46 H 4.78 N 18.91.

6.2.2. N-(3-Nitrophenyl)-4-(pyridin-3-yl)-1H-imidazol-2-amine (*5b*)

Yield: 9.19 g, 32.70 mmol (66%) of yellow crystals, mp: 191.8–192.0 °C. IR (KBr): ν (cm^{-1}) = 3406, 3099, 1600, 1526. ^1H NMR (DMSO-d_6): δ (ppm) = 6.00 (s, br., 2H), 7.37 (dd, 1H, J = 7.8 Hz, J = 4.9 Hz), 7.73 (s, 1H), 7.83 (t, 1H, J = 8.2 Hz), 8.06–8.00 (m, 2H), 8.23 (ddd, 1H, J = 8.2 Hz, J = 2.2 Hz, J = 0.8 Hz), 8.39–8.37 (m, 2 H), 8.95 (d, 1H, J = 1.7 Hz). CI-MS (NH_3) *m/z* (%): 252 (100), 282 (25) $[M - H^+]^-$. Anal. ($C_{14}H_{11}N_5O_2 \cdot 1/2H_2O$): C, H, N.

6.2.3. N-(2-Methyl-5-nitrophenyl)-4-(pyridin-3-yl)-1H-imidazol-2-amine (*5c*)

Yield: 3.45 g (50%), yellow crystals, mp: 153.0–154.0 °C. IR (KBr): ν (cm^{-1}) = 3432, 3084, 1629, 1522. ^1H NMR (DMSO-d_6): δ (ppm) = 2.27 (s, 3H), 5.74 (s, 2H, exchangeable), 7.34 (dd, 1H, J = 7.7 Hz, J = 4.7 Hz, aromat.), 7.45 (s, 1H, aromat.), 7.73 (d, 1H, J = 8.5 Hz aromat.), 8.00 (d, 1H, J = 7.7 Hz, aromat.), 8.16 (d, 1H, J = 2.5 Hz, aromat.), 8.27 (dd, 1H, J = 8.5 Hz, J = 2.5 Hz, aromat.), 8.36 (dd, 1H, J = 4.7 Hz, J = 1.6 Hz, aromat.), 8.91 (d, 1H, J = 1.6 Hz, aromat.). EI-MS (70 eV) *m/z* (%): 295 (100) $[M]^{+\bullet}$, 265 (5), 249 (6). Anal. ($C_{15}H_{13}N_5O_2$): C, H, N.

*6.2.4. N-(2-Ethyl-5-nitrophenyl)-4-(pyridin-3-yl)-1H-imidazol-2-amine (**5d**)*

Yield: 2.93 g, 9.47 mmol (41%) of yellow crystals, mp: 166.9–167.0 °C. IR (KBr): ν (cm^{-1}) = 3301, 3129, 1635, 1521. ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.12 (t, 3H, J = 7.5 Hz), 2.59 (q, 2H, J = 7.5 Hz), 5.71 (s, 2H), 7.34 (dd, 1H, J = 7.9 Hz, J = 4.7 Hz, aromat.), 7.45 (s, 1H, aromat.), 7.75 (d, 1H, J = 8.8 Hz, aromat.), 8.00 (td, 1H, J = 8.1 Hz, J = 2.0 Hz, aromat.), 8.14 (d, 1H, J = 2.5 Hz, aromat.), 8.30–8.37 (m, 2H, aromat.), 8.91 (d, 1H, J = 1.4 Hz, aromat.). CI-MS (NH_3) *m/z* (%): 310 (27) $[M + H^+]^+$, 280 (100). Anal. ($C_{16}H_{15}N_5O_2 \cdot 1/4H_2O$): C, H, N.

*6.2.5. N-(2-Methyl-5-nitrophenyl)-4-(pyridin-4-yl)-1H-imidazol-2-amine (**5e**) [11]*

Yield: 1.82 g (21%), yellow crystals, mp: 156.9–157.2 °C. IR (KBr): ν (cm^{-1}) = 3252, 3107, 1665, 1599. ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.26 (s, 3H), 5.78 (s, 2H, exchangeable), 7.60 (AA′, 2H, aromat.), 7.62 (s, 1H, aromat.), 7.74 (d, 1H, J = 8.5 Hz aromat.), 8.18 (d, 1H, J = 2.5 Hz aromat.), 8.28 (dd, 1H, J = 8.5 Hz, J = 2.5 Hz, aromat.), 8.46 (XX′, 2H, aromat.). Anal. ($C_{15}H_{13}N_5O_2$): C, H, N.

*6.3. Preparation of compounds **6a–6e** by catalytic reduction of the nitro group – general procedure B*

To a stirred solution of the respective nitro precursor **5a–5e** (5.00 mmol) and NH_4HCOO (50.0 mmol) in methanol (100 mL), Pd on charcoal (10%, 0.5 g) was added and the mixture heated to 60 °C for 15–30 min until an excessive gas development occurred. The hot solution was filtered over a pad of Na_2SO_4 to remove the catalyst, and the solvent was distilled off under reduced pressure. In case of **6b–6e**, the remaining solid was dissolved in CH_2Cl_2, extracted with diluted aqueous ammonia, the organic layer dried (Na_2SO_4), the solvent removed, and the product purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 10:1). In case of **6a**, the crude solid was directly subjected to column chromatography (SiO_2; CH_2Cl_2/MeOH, 10:1).

*6.3.1. 6-Methyl-N^1-(4-phenyl-1H-imidazol-2-yl)benzene-1,3-diamine formate (**6a**)*

Yield: 1.08 g (82%), colorless solid, mp: 156.6–160.0 °C. IR (KBr): ν (cm^{-1}) = 3459, 3197, 1670. ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.94 (s, 3H), 5.30 (s, vbr., 2H, exchangeable), 5.46 (s, 3H, exchangeable), 6.49 (d, 1H, J = 2.4 Hz, aromat.), 6.59 (dd, 1H, J = 8.2 Hz, J = 2.4 Hz, aromat.), 7.02 (d, 1H, J = 8.2 Hz, aromat.), 7.15–7.16 (m, 1H, aromat.), 7.17 (s, 1H, aromat.), 7.28–7.32 (m, 2H, aromat.), 7.66–7.69 (m, 2H, aromat.), 8.18 (s, 1H). EI-MS (70 eV) *m/z* (%): 264 (100) $[M]^{+\bullet}$, 221 (13), 161 (26), 146 (28), 132 (17). Anal. ($C_{16}H_{16}N_4 \cdot HCOOH$): C, H, N.

*6.3.2. N-(4-Pyridin-3-yl-1H-imidazol-2-yl)-benzene-1,3-diamine (**6b**)*

Yield: 1.46 g (81%), yellow crystals, mp: 129.5–129.6 °C. IR (KBr): ν (cm^{-1}) = 3386, 3091, 1601. ^{1}H NMR (DMSO-d_6): δ (ppm) = 5.39 (s, 2H), 5.55 (s, 2H), 6.57 (dd, 2H, J = 1.1 Hz, J = 7.9 Hz, aromat.), 6.65 (t, 1H, J = 2.0 Hz, aromat.), 7.14 (t, 1H, J = 7.9 Hz, aromat.), 7.32 (dd, 1H, J = 4.7 Hz, J = 7.9 Hz, aromat.), 7.45 (s, 1H, aromat.), 8.00 (td, 1H, J = 1.9 Hz, J = 7.9 Hz, aromat.), 8.33 (dd, 1H, J = 1.6 Hz, J = 4.7 Hz, aromat.), 8.91 (d, 1H, J = 1.6 Hz, aromat.). CI-MS (NH_3) *m/z* (%): 252 (100) $[M + H^+]^+$. Anal. ($C_{14}H_{13}N_5 \cdot 1/4H_2O$): C, H, N.

*6.3.3. 6-Methyl-N^1-(4-(pyridin-3-yl)-1H-imidazol-2-yl)benzene-1,3-diamine (**6c**)*

Yield: 1.06 g (80%), colorless crystals, mp: 121.9–122.4 °C. IR (KBr): ν (cm^{-1}) = 3340, 3217, 1619. ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.94 (s, 3H), 5.17 (s, br., 2H, exchangeable), 5.32 (s, 2H, exchangeable), 6.49 (d, 1H, J = 2.4 Hz, aromat.), 6.59 (dd, 1H, J = 8.2 Hz, J = 2.4 Hz, aromat.), 7.02 (d, 1H, J = 8.2 Hz, aromat.), 7.30 (s, 1H, aromat.), 7.31 (ddd, 1H, J = 7.9 Hz, J = 4.8 Hz, J = 0.9 Hz, aromat.), 7.98 (ddd, 1H, J = 7.9 Hz, J = 1.7 Hz, J = 2.2 Hz, aromat.), 8.32 (dd, 1H, J = 4.8 Hz, J = 1.7 Hz, aromat.), 8.90 (d, 1H, J = 2.2 Hz, J = 0.9 Hz, aromat.). CI-MS (NH_3) *m/z* (%): 266 (100) $[M + H^+]^+$. Anal. ($C_{15}H_{15}N_5 \cdot H_2O$): C, H, N.

*6.3.4. 4-Ethyl-N-(4-pyridin-3-yl-1H-imidazol-2-yl)-benzene-1,3-diamine (**6d**)*

Yield: 1.31 g (61%), yellow crystals, mp: 162.6–162.8 °C. IR (KBr): ν (cm^{-1}) = 3346, 3127, 1601. ^{1}H NMR (DMSO-d_6): δ (ppm) = 0.99 (t, 3H, J = 7.5 Hz), 2.28 (q, v br., 2H, J = 8.6 Hz), 5.19 (s, br., 2H), 5.28 (s, br., 2H), 6.45 (d, 1H, J = 2.2 Hz, aromat.), 6.63 (dd, 1H, J = 8.2 Hz, J = 2.2 Hz, aromat.), 7.05 (d, 1H, J = 8.23 Hz, aromat.), 7.30 (m, 2H, aromat.), 7.98 (td, 1H, J = 8.1 Hz, J = 2.0 Hz, aromat.), 8.31 (dd, 1H, J = 4.7 Hz, J = 1.6 Hz, aromat.), 8.89 (d, 1H, J = 1.4 Hz, aromat.). CI-MS (NH_3) *m/z* (%): 280 (100) $[M + H^+]^+$. Anal. ($C_{16}H_{17}N_5 \cdot 1/4H_2O$): C, H, N.

*6.3.5. 6-Methyl-N^1-(4-(pyridin-4-yl)-1H-imidazol-2-yl)benzene-1,3-diamine (**6e**) [11]*

Yield: 1.29 g (97%), colorless solid.

*6.4. Preparation of amides **8a**, **8b**, **8k**, **9a–9l**, **10c**, **10d**, **10l**, **11b–11e**, **12b** and **12l** – general procedure C*

The amidations of the arylamines **6a–6e** were performed with the respective free base. In case of **6a**, this was obtained by subjecting the formamidinium salt to the following procedure: the salt was dissolved in CH_2Cl_2, the organic layer extracted with diluted aqueous ammonia, the organic layer dried (Na_2SO_4), and the solvent removed.

Amidation procedure of the arylamines: to a stirred solution of the respective arylamine (1.0 mmol) in pyridine (20.0 mL), the respective carboxylic acid chloride (**7a–7j**), 4-(pyridin-4-yl)benzoyl chloride hydrochloride (**7k**) or 4′-((4-methylpiperazin-1-yl)methyl)biphenyl-4-carbonyl chloride dihydrochloride (**7l**) (1.1 mmol) was added, and the mixture stirred at room temperature for 1–2 h. NaH (1.1 mmol) was added and the

mixture stirred for additional 12 h. If carbonic acid chloride hydrochlorides were used for amidation, additional 1.1 equiv of NaH were added for each hydrochloride equivalent. The solvent was removed under reduced pressure, the residue treated with diluted aqueous ammonia (30 mL), extracted with CH_2Cl_2 (3 × 50 mL), the organic layer dried (Na_2SO_4) and the solvent removed.

Purification was performed by column chromatography (**7l**, **8l**, **9l**, **10l** and **12l**: SiO_2; CH_2Cl_2/MeOH/NH_3 conc. 3:1:0.01; all other compounds: CH_2Cl_2/MeOH/NH_3 conc. 10:1:0.01), yielding the desired amides as colorless solids.

*6.4.1. N-(4-Methyl-3-(4-phenyl-1H-imidazol-2-ylamino)phenyl)acetamide (**8a**)*

Yield: 0.14 g (24%), mp: 191.6–192.9 °C. IR (KBr): ν (cm^{-1}) = 3311, 1681, 1604. ^1H NMR (DMSO-d_6): δ (ppm) = 2.06 (d, 6H, J = 6.6 Hz), 5.37 (s, 2H), 7.13 (t, 1H, J = 7.3 Hz, aromat.), 7.19 (s, 1H, aromat.), 7.30 (t, 3H, J = 7.5 Hz, aromat.), 7.54 (dd, 1H, J = 2.0 Hz, J = 8.2 Hz, aromat.), 7.60 (d, 1H, J = 2.0 Hz, aromat.), 7.68 (d, 2H, J = 7.1 Hz, aromat.), 10.08 (s, 1H). PI-EIMS (70 eV) *m/z* (%): 306 (100) $[M]^{+\bullet}$, 160 (39). Anal. ($C_{18}H_{18}N_4O \cdot 1/3H_2O$): C, H, N.

*6.4.2. N-(4-Methyl-3-(4-phenyl-1H-imidazol-2-ylamino)phenyl)benzamide (**8b**)*

Yield: 0.27 g (39%), mp: 191.4–193.0 °C. IR (KBr): ν (cm^{-1}) = 3380, 2922, 1650, 1615. ^1H NMR (DMSO-d_6): δ (ppm) = 2.12 (s, 3H), 5.40 (s, 2H), 7.14 (t, 1H, J = 7.3 Hz, aromat.), 7.23 (s, 1H), 7.31 (t, 2H, J = 7.7 Hz, aromat.), 7.38 (d, 1H, J = 9.0 Hz, aromat.), 7.50–7.69 (m, 3H, aromat.), 7.70 (d, 2H, J = 7.2 Hz, aromat.), 7.82 (dd, 2H, J = 2.2 Hz, J = 4.2 Hz, aromat.), 7.95 (d, 2H, J = 6.7 Hz, aromat.), 10.39 (s, 1H). PI-EIMS (70 eV) *m/z* (%): 368 (100) $[M]^{+\bullet}$. Anal. ($C_{23}H_{20}N_4O \cdot 1/2H_2O$): C, H, N.

*6.4.3. N-(4-Methyl-3-(4-phenyl-1H-imidazol-2-ylamino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (**8l**)*

Yield: 0.13 g (28%), mp: 126.0–131.0 °C. IR (KBr): ν (cm^{-1}) = 3325, 2950, 2805, 1659. ^1H NMR (DMSO-d_6): δ (ppm) = 2.11 (s, 3H), 2.18 (s, 3H), 2.39 (s, br., 8H), 3.54 (s, 2H), 5.37 (s, 2H, exchangeable), 7.13–7.19 (m, 1H, aromat.), 7.22 (s, 1H, aromat.), 7.29–7.35 (m, 2H, aromat.), 7.38–7.40 (m, 1H, aromat.), 7.44–7.47 (AA′, 2H, aromat.), 7.68–7.72 (m, 2H, aromat.), 7.78–7.82 (m, 2H, aromat.), 7.89–7.92 (BB′, 2H, aromat.), 10.33 (s, 1H, exchangeable). ESI-MS (CH_2Cl_2, MeOH, 10 mmol L^{-1} NH_4Ac) *m/z* (%): 481 (100) $[M + H^+]^+$. Anal. ($C_{29}H_{32}N_6O \cdot 3H_2O$): C, H, N.

*6.4.4. N-(4-Methyl-3-(4-(pyridin-3-yl)-1H-imidazol-2-ylamino)phenyl)acetamide (**9a**)*

Yield: 0.18 g (35%), mp: 140.9–146.2 °C. IR (KBr): ν (cm^{-1}) = 3305, 2365, 1671, 1601. ^1H NMR (DMSO-d_6): δ (ppm) = 2.06 (d, 6H, J = 6.8 Hz), 5.48 (s, 2H), 7.54 (dd, 1H, J = 2.1 Hz, J = 8.4 Hz, aromat.), 7.62 (d, 1H, J = 2.1 Hz, aromat.), 7.30–7.37 (m, 3H, aromat.), 7.99 (td, 1H, J = 2.0 Hz, J = 8.0 Hz, aromat.), 8.34 (dd, 1H, J = 1.6 Hz, J = 8.4 Hz, aromat.), 8.91 (d, 1H, J = 1.7 Hz, aromat.), 10.07 (s, 1H). EI-MS (70 eV) *m/z* (%): 307 (100) $[M]^{+\bullet}$, 160 (44). Anal. ($C_{17}H_{17}N_5O \cdot 2/3H_2O$): C, H, N.

*6.4.5. N-(4-Methyl-3-(4-(pyridin-3-yl)-1H-imidazol-2-ylamino)phenyl)benzamide (**9b**)*

Yield: 0.22 g (42%), mp: 240.2–240.9 °C. IR (KBr): ν (cm^{-1}) = 3435, 2924, 2854, 1668, 1604. ^1H NMR (DMSO-d_6): δ (ppm) = 2.12 (s, 3H), 5.53 (s, 2H), 7.33 (dd, 1H, J = 4.8 Hz, J = 7.3 Hz, aromat.), 7.38 (d, 2H, J = 5.0 Hz, aromat.), 7.51–7.63 (m, 3H), 7.82 (dd, 2H, J = 2.0 Hz, J = 7.0 Hz, aromat.), 7.95 (dd, 2H, J = 1.5 Hz, J = 8.1 Hz, aromat.), 8.01 (td, 1H, J = 2.0 Hz, J = 8.0 Hz, aromat.), 8.34 (dd, 1H, J = 1.6 Hz, J = 4.7 Hz, aromat.), 8.92 (d, 1H, J = 1.7 Hz, aromat.), 10.39 (s, 1H). PI-EIMS (70 eV) *m/z* (%): 369 (100) $[M]^{+\bullet}$, 105 (56), 77 (30), 160 (15). Anal. ($C_{22}H_{19}N_5O \cdot H_2O$): C, H, N.

*6.4.6. 2-Methyl-N-(4-methyl-3-(4-(pyridin-3-yl)-1H-imidazol-2-ylamino)phenyl)benzamide (**9c**)*

Yield: 0.45 g (59%), white crystals, mp: 117.6–118.2 °C. IR (KBr): ν (cm^{-1}) = 3432, 2924, 1669, 1616. ^1H NMR (DMSO-d_6): δ (ppm) = 2.10 (s, 3H), 2.38 (s, 3H), 5.53 (s, 2H), 7.25–7.47 (m, 7H, aromat.), 7.76 (ddd, 2H, J = 8.1 Hz, J = 8.1 Hz, aromat.), 8.01 (td, 1H, J = 7.7 Hz, J = 1.6 Hz, aromat.), 8.34 (dd, 1H, J = 4.7 Hz, J = 1.4 Hz, aromat.), 8.92 (d, 1H, J = 1.6 Hz, aromat.), 10.47 (s, 1H). CI-MS (NH_3) *m/z* (%): 384 (100) $[M + H^+]^+$. Anal. ($C_{23}H_{21}N_5O \cdot 1/2H_2O$): C, H, N.

*6.4.7. 3-Methyl-N-(4-methyl-3-(4-(pyridin-3-yl)-1H-imidazol-2-ylamino)phenyl)benzamide (**9d**)*

Yield: 0.13 g (17%), white crystals, mp: 151.9–153.2 °C. IR (KBr): ν (cm^{-1}) = 3322, 2921, 1663, 1599. ^1H NMR (DMSO-d_6): δ (ppm) = 2.12 (s, 3H), 2.40 (s, 3H), 5.53 (s, 2H), 7.26–7.47 (m, 5H, aromat.), 7.71–7.86 (m, 4H, aromat.), 8.01 (td, 1H, J = 7.0 Hz, J = 1.4 Hz, aromat.), 8.34 (dd, 1H, J = 4.7 Hz, J = 1.4 Hz, aromat.), 8.92 (d, 1H, J = 2.0 Hz, aromat.), 10.34 (s, 1H). CI-MS (NH_3) *m/z* (%): 384 (100) $[M + H^+]^+$. Anal. ($C_{23}H_{21}N_5O \cdot 1/3H_2O$): C, H, N.

*6.4.8. 4-Methyl-N-(4-methyl-3-(4-(pyridin-3-yl)-1H-imidazol-2-ylamino)phenyl)benzamide (**9e**)*

Yield: 0.68 g (94%), mp: 202.6–202.7 °C. IR (KBr): ν (cm^{-1}) = 1653, 1610. ^1H NMR (DMSO-d_6): δ (ppm) = 2.11 (s, 3H), 2.93 (s, 3H), 5.51 (s, 2H), 7.30–7.40 (m, 5H, aromat.), 7.80–7.90 (m, 4H, aromat.), 8.01 (td, 1H, J = 1.8 Hz, J = 8.0 Hz, aromat.), 8.34 (dd, 1H, J = 1.6 Hz, J = 4.7 Hz, aromat.), 8.92 (d, 1H, J = 1.6 Hz, aromat.), 10.30 (s, 1H). EI-MS (70 eV) *m/z* (%): 119 (100), 383 (71) $[M]^+$, 91 (42), 160 (13). Anal. ($C_{23}H_{21}N_5O$): C, H, N.

*6.4.9. 4-Decyl-N-(4-methyl-3-(4-(pyridin-3-yl)-1H-imidazol-2-ylamino)phenyl)benzamide (**9f**)*

Yield: 0.68 g (71%), mp: 109.3–109.8 °C. IR (KBr): ν (cm^{-1}) = 3442, 2925, 2854, 1671, 1611. ^1H NMR (DMSO-d_6): δ (ppm) = 0.85 (t, 3H, J = 6.7 Hz), 1.24 (s, br., 14H),

1.59 (s, 2H), 2.11 (s, 3H), 2.65 (t, 2H, $J = 7.5$ Hz), 5.50 (s, 2H), 7.30–7.42 (m, 5H, aromat.), 7.79–7.91 (m, 4H, aromat.), 8.01 (d, 1H, $J = 7.9$ Hz), 8.34 (dd, 1H, $J = 1.3$ Hz, $J = 4.6$ Hz, aromat.), 8.92 (d, 1H, $J = 1.7$ Hz, aromat.), 10.41 (s, 1H). EI-MS (70 eV) *m/z* (%): 509 (100) $[M]^{+\bullet}$ 245 (58). Anal. ($C_{32}H_{39}N_5O \cdot 1/4C_4H_8O_2$): C, H, N.

*6.4.10. 4-Methoxy-N-(4-methyl-3-(4-(pyridin-3-yl)-1H-imidazol-2-ylamino)phenyl)benzamide (**9g**)*

Crystallisation from diethyl ether. Yield: 0.48 g (28%), mp: 196.1–198.8 °C. IR (KBr): ν (cm^{-1}) = 3433, 2838, 1659, 1605. ^1H NMR (DMSO-d_6): δ (ppm) = 2.11 (s, 3H), 3.84 (s, 3H), 5.50 (s, 2H), 7.07 (d, 2H, $J = 9.0$ Hz, aromat.), 7.30–7.40 (m, 3H), 7.82 (dd, 2H, $J = 2.1$ Hz, $J = 6.0$ Hz, aromat.), 7.93–8.03 (m, 3H), 8.34 (dd, 1H, $J = 1.6$ Hz, $J = 4.7$ Hz, aromat.), 8.92 (d, 1H, $J = 1.7$ Hz, aromat.), 10.23 (s, 1H). PI-EIMS (70 eV) *m/z* (%): 399 (100) $[M]^{+\bullet}$, 135 (95). Anal. ($C_{23}H_{21}N_5O_2 \cdot 1/4\ C_4H_{10}O$): C, H, N.

*6.4.11. 3,4,5-Trimethoxy-N-(4-methyl-3-(4-(pyridin-3-yl)–1H-imidazol-2-ylamino)phenyl)benzamide (**9h**)*

Yield: 0.24 g (28%), mp: 221.7–222.8 °C. IR (KBr): ν (cm^{-1}) = 3451, 1653, 1616. ^1H NMR (DMSO-d_6): δ (ppm) = 2.12 (s, 3H), 3.73 (s, 3H), 3.87 (s, 6H), 5.51 (s, 2H), 7.28 (s, 2H, aromat.), 7.33 (dd, 1H, $J = 4.5$ Hz, $J = 8.2$ Hz, aromat.), 7.41 (d, 2H, $J = 7.3$ Hz, aromat.), 7.76 (d, 1H, $J = 2.1$ Hz, aromat.), 7.84 (dd, 1H, $J = 2.1$ Hz, $J = 8.3$ Hz, aromat.), 8.01 (td, 1H, $J = 2.0$ Hz, $J = 8.0$ Hz, aromat.), 8.34 (dd, 1H, $J = 1.6$ Hz, $J = 4.8$ Hz, aromat.), 8.92 (d, 1H, $J = 1.6$ Hz, aromat.), 10.23 (s, 1H). EI-MS (70 eV) *m/z* (%): 195 (100), 459 (50) $[M]^{+\bullet}$. Anal. ($C_{25}H_{25}N_5O_4 \cdot 1/4H_2O$): C, H, N.

*6.4.12. N-(4-Methyl-3-(4-(pyridin-3-yl)-1H-imidazol-2-ylamino)phenyl)-4-nitrobenzamide (**9i**)*

Yield: 0.74 g (95%), yellow crystals, mp: 191.6–195.7 °C. IR (KBr): ν (cm^{-1}) = 3383, 2923, 2795, 1664, 1600. ^1H NMR (DMSO-d_6): δ (ppm) = 2.13 (s, 3H), 5.53 (s, 2H), 7.33 (dd, 1H, $J = 4.8$ Hz, $J = 8.0$ Hz, aromat.), 7.39–7.45 (m, 2H), 7.82 (dd, 2H, $J = 2.1$ Hz, $J = 6.4$ Hz, aromat.), 8.01 (td, 1H, $J = 2.0$ Hz, $J = 8.0$ Hz, aromat.), 8.19 (d, 2H, $J = 8.8$ Hz, aromat.), 8.33–8.42 (m, 3H), 8.92 (d, 1H, $J = 1.6$ Hz, aromat.), 10.71 (s, 1H). PI-EIMS (70 eV) *m/z* (%): 414 (100) $[M]^{+\bullet}$. Anal. ($C_{22}H_{18}N_6O_3 \cdot H_2O$): C, H, N.

*6.4.13. 4-Chloro-N-(4-methyl-3-(4-(pyridin-3-yl)-1H-imidazol-2-ylamino)phenyl)benzamide (**9j**)*

Crystallisation from ethyl acetate. Yield: 0.39 g (51%), mp: 241.8–243.5 °C. IR (KBr): ν (cm^{-1}) = 3424, 1649, 1602. ^1H NMR (DMSO-d_6): δ (ppm) = 2.12 (s, 3H), 5.55 (s, 2H), 7.33 (dd, 1H, $J = 4.9$ Hz, $J = 7.8$ Hz, aromat.), 7.40 (t, 2H, $J = 4.5$ Hz, aromat.), 7.63 (d, 2H, $J = 8.6$ Hz, aromat.), 7.81 (d, 2H, $J = 6.6$ Hz, aromat.), 7.96–8.03 (m, 3H), 8.34 (dd, 1H $J = 1.5$ Hz, $J = 4.7$ Hz, aromat.), 8.92 (d, 1H, $J = 1.7$ Hz, aromat.), 10.46 (s, 1H). EI-MS (70 eV) *m/z* (%): 139 (100), 403 (96) $[M]^{+\bullet}$, 111 (45). Anal. ($C_{22}H_{18}ClN_5O \cdot 1/4C_4H_8O_2$): C, H, N.

*6.4.14. N-(4-Methyl-3-(4-(pyridin-3-yl)-1H-imidazol-2-ylamino)phenyl)isonicotinamide (**9k**)*

Crystallisation from ethyl acetate. Yield: 0.39 g (56%), mp: 261.5–262.9 °C. IR (KBr): ν (cm^{-1}) = 3404, 1666, 1603. ^1H NMR (DMSO-d_6): δ (ppm) = 2.13 (s, 3H), 5.53 (s, 2H), 7.33 (dd, 1H, $J = 5.0$ Hz, $J = 7.5$ Hz, aromat.), 7.39–7.44 (m, 2H), 7.79–7.89 (m, 4H, aromat.), 8.01 (td, 1H, $J = 2.0$ Hz, $J = 8.0$ Hz, aromat.), 8.34 (dd, 1H, $J = 1.6$ Hz, $J = 4.7$ Hz, aromat.), 8.80 (dd, 2H, $J = 1.6$ Hz, $J = 4.4$ Hz, aromat.), 8.92 (d, 1H, $J = 1.6$ Hz, aromat.), 10.64 (s, 1H). PI-EIMS (70 eV) *m/z* (%): 370 (100) $[M]^{+\bullet}$, 78 (16), 106 (14). Anal. ($C_{21}H_{18}N_6O \cdot 1/4C_4H_8O_2$): C, H, N.

*6.4.15. N-(4-Methyl-3-(4-(pyridin-3-yl)-1H-imidazol-2-ylamino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (**9l**)*

Yield: 0.18 g (38%), mp: 230.1–232.0 °C. IR (KBr): ν (cm^{-1}) = 2945, 2809, 1639. ^1H NMR (DMSO-d_6): δ (ppm) = 2.11 (s, 3H), 2.15 (s, 3H), 2.35 (s, br., 8H), 3.53 (s, 2H), 5.50 (s, 2H, exchangeable), 7.31–7.40 (m, 2H, aromat.), 7.39 (s, 1H, aromat.), 7.44–7.46 (AA′, 2H, aromat.), 7.80–7.83 (m, 2H, aromat.), 7.89–7.92 (BB′, 2H, aromat.), 7.99–8.03 (m, 1H, aromat.), 8.33–8.35 (m, 1H, aromat.), 8.92–8.93 (m, 1H, aromat.), 10.36 (s, 1H, exchangeable). EI-MS (70 eV) *m/z* (%): 481 (17) $[M]^{+\bullet}$, 466 (10), 425 (21), 411 (94), 383 (100), 118 (79), 99 (52), 90 (78). Anal. ($C_{28}H_{31}N_7O \cdot 2H_2O$): C, H, N.

*6.4.16. 4-Amino-N-(4-methyl-3-(4-(pyridin-3-yl)-1H-imidazol-2-ylamino)phenyl)benzamide (**9m**)*

Preparation was performed from **9i** by catalytic reduction of the nitro group according to general procedure B as described for **6b–6e**: crystallisation from ethyl acetate. Yield: 0.16 g (41%), mp: 161.9–167.9 °C. IR (KBr): ν (cm^{-1}) = 3442, 1658, 1603. ^1H NMR (DMSO-d_6): δ (ppm) = 2.10 (s, 3H), 5.51 (s, 2H), 5.79 (s, 2H), 6.60 (d, 2H, $J = 8.6$ Hz, aromat.), 7.30–7.40 (m, 3H), 7.71 (d, 2H, $J = 8.8$ Hz, aromat.), 7.80 (d, 2H, $J = 7.41$ Hz, aromat.), 8.01 (td, 1H, $J = 1.8$ Hz, $J = 8.0$ Hz, aromat.), 8.34 (dd, 1H, $J = 1.5$ Hz, $J = 4.7$ Hz, aromat.), 8.92 (d, 1H, $J = 1.6$ Hz, aromat.), 9.91 (s, 1H). PI-EIMS (70 eV) *m/z* (%): 120 (100), 384 (87) $[M]^{+\bullet}$. Anal. ($C_{22}H_{20}N_6O \cdot 1/3C_4H_8O_2$): C, H, N.

*6.4.17. 2-Methyl-N-(3-(4-(pyridin-3-yl)-1H-imidazol-2-ylamino)phenyl)benzamide (**10c**)*

Yield: 0.33 g (45%), white crystals, mp: 116.1–116.3 °C. IR (KBr): ν (cm^{-1}) = 3425, 3061, 1665, 1601. ^1H NMR (DMSO-d_6): δ (ppm) = 2.40 (s, 3H), 5.72 (s, 2H), 7.23–7.55 (m, 8H, aromat.), 7.76 (d, 1H, $J = 7.4$ Hz, aromat.), 7.95 (s, v br., 1H, aromat.), 8.02 (td, 1H, $J = 8.1$ Hz, $J = 2.0$ Hz, aromat.), 8.35 (dd, 1H, $J = 4.8$ Hz, $J = 1.5$ Hz, aromat.), 8.93 (d, 1H, $J = 1.6$ Hz, aromat.), 10.53 (s, 1H). CI-MS (NH_3) *m/z* (%): 370 (100) $[M + H^+]^+$. Anal. ($C_{22}H_{19}N_5O \cdot 3/4H_2O$): C, H, N.

*6.4.18. 3-Methyl-N-(3-(4-(pyridin-3-yl)-1H-imidazol-2-ylamino)phenyl)benzamide (**10d**)*

Yield: 0.16 g (22%), white crystals, mp: 120.3–120.6 °C. IR (KBr): ν (cm^{-1}) = 3422, 3065, 1652, 1603. ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.41 (s, 3H), 5.74 (s, 2H), 7.23 (dd, 1H, J = 7.7 Hz, J = 1.6 Hz, aromat.), 7.35 (dd, 1H, J = 7.9 Hz, J = 4.9 Hz, aromat.), 7.42–7.57 (m, 4H, aromat.), 7.75–7.86 (m, 3H, aromat.), 8.00 (ttt, 2H, J = 9.1 Hz, J = 1.7 Hz, aromat.), 8.36 (dd, 1H, J = 4.7 Hz, J = 1.6 Hz, aromat.), 8.94 (d, 1H, J = 1.9 Hz, aromat.), 10.42 (s, 1H). CI-MS (NH_3) *m/z* (%): 370 (100) $[M + H^+]^+$. Anal. ($C_{22}H_{19}N_5O \cdot H_2O$): C, H, N.

*6.4.19. 4-Methyl-N-(3-(4-(pyridin-3-yl)-1H-imidazol-2-ylamino)phenyl)benzamide (**10e**)*

Yield: 0.17 g (23%), white crystals, mp: 218.8–219.0 °C. IR (KBr): ν (cm^{-1}) = 3440, 3126, 1665, 1598. ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.39 (s, 3H), 5.74 (s, 2H), 7.23 (dd, 1H, J = 8.0 Hz, J = 1.4 Hz, aromat.), 7.32–7.38 (m, 3H, aromat.), 7.48–7.57 (m, 2H, aromat.), 7.82–7.93 (m, 3H, aromat.), 8.01 (ttt, 2H, J = 7.7 Hz, J = 2.0 Hz, aromat.), 8.35 (dd, 1H, J = 4.7 Hz, J = 1.6 Hz, aromat.), 8.94 (d, 1H, J = 2.0 Hz, aromat.), 10.37 (s, 1H). CI-MS (NH_3) *m/z* (%): 370 (100) $[M + H^+]^+$. Anal. ($C_{22}H_{19}N_5O$): C, H, N.

*6.4.20. 4-((4-Methylpiperazin-1-yl)methyl)-N-(3-(4-(pyridin-3-yl)-1H-imidazol-2-ylamino) phenyl)benzamide (**10l**)*

Yield: 0.43 g (58%), white crystals, mp: 150.9–151.2 °C. IR (KBr): ν (cm^{-1}) = 3324, 2941, 1651, 1603. ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.15 (s, 3H), 2.37 (s, v br., 8H), 3.54 (s, 2H), 5.73 (s, 2H), 7.23 (dd, 1H, J = 8.0 Hz, J = 1.4 Hz, aromat.), 7.34 (ddd, 1H, J = 8.1 Hz, J = 6.0 Hz, aromat.), 7.44–7.56 (m, 4H), 7.84 (dd, 1H, J = 8.2 Hz, J = 1.1 Hz, aromat.), 7.93 (d, 2H, J = 8.5 Hz, aromat.), 8.01 (ttt, 2H, J = 8.2 Hz, J = 2.0 Hz, aromat.), 8.36 (dd, 1H, J = 4.7 Hz, J = 1.6 Hz, aromat.), 8.94 (d, 1H, J = 1.4 Hz, aromat.), 10.42 (s, 1H). CI-MS (NH_3) *m/z* (%): 468 (100) $[M + H^+]^+$. Anal. ($C_{27}H_{29}N_7O \cdot H_2O$):C, H, N.

*6.4.21. N-(4-Ethyl-3-(4-(pyridin-3-yl)-1H-imidazol-2-ylamino)phenyl)benzamide (**11b**)*

Yield: 0.48 g (63%), white crystals, mp: 165.8–166.4 °C. IR (KBr): ν (cm^{-1}) = 3436, 2966, 1667, 1604. ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.08 (t, 3H, J = 7.5 Hz), 2.44 (q, br., 2H, J = 7.4 Hz), 5.49 (s, 2H), 7.33 (dd, 1H, J = 8.0 Hz, J = 4.7 Hz, aromat.), 7.42 (d, 2H, J = 10.4 Hz, aromat.), 7.51–7.63 (m, 3H, aromat.), 7.81 (d, 1H, J = 2.0 Hz), 7.88 (dd, 1H, J = 8.5 Hz, J = 2.2 Hz, aromat.), 7.96 (dd, 2H, J = 8.1 Hz, J = 1.5 Hz, aromat.), 8.01 (td, 1H, J = 7.6 Hz, J = 2.0 Hz, aromat.), 8.34 (dd, 1H, J = 4.8 Hz, J = 1.5 Hz, aromat.), 8.92 (d, 1H, J = 1.6 Hz, aromat.), 10.41 (s, 1H). CI-MS (NH_3) *m/z* (%): 384 (100) $[M + H^+]^+$. Anal. ($C_{23}H_{21}N_5O \cdot 2/5H_2O$): C, H, N.

*6.4.22. N-(4-Ethyl-3-(4-(pyridin-3-yl)-1H-imidazol-2-ylamino)phenyl)-2-methylbenzamide (**11c**)*

Yield: 0.49 g (62%), white crystals, mp: 120.3–122.3 °C. IR (KBr): ν (cm^{-1}) = 3440, 2968, 1659, 1616. ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.07 (t, 3H, J = 7.5 Hz), 2.39 (s, 3H), 2.44 (q, 2H, J = 5.0 Hz), 5.49 (s, 2H), 7.28–7.47 (m, 7H, aromat.), 7.75–7.81 (m, 2H, aromat.), 8.00 (td, 1H, J = 8.0 Hz, J = 2.0 Hz, aromat.), 8.34 (dd, 1H, J = 4.7 Hz, J = 1.6 Hz, aromat.), 8.92 (d, 1H, J = 1.6 Hz), 10.47 (s, 1H). CI-MS (NH_3) *m/z* (%): 398 (100) $[M + H^+]^+$. Anal. ($C_{24}H_{23}N_5O \cdot 2/3H_2O$): C, H, N.

*6.4.23. N-(4-Ethyl-3-(4-(pyridin-3-yl)-1H-imidazol-2-ylamino)phenyl)-3-methylbenzamide (**11d**)*

Yield: 0.47 g (59%), white crystals, mp: 161.7–163.2 °C. IR (KBr): ν (cm^{-1}) = 3436, 2965, 1667, 1600. ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.08 (t, 3H, J = 7.5 Hz), 2.40 (s, 3H), 2.45 (q, br., 2H, J = 7.1 Hz), 5.48 (s, 2H), 7.30–7.37 (m, 1H, aromat.), 7.39–7.44 (m, 4H, J = 8.5 Hz, aromat.), 7.72–7.81 (m, 3H, aromat.), 7.88 (dd, 1H, J = 8.5 Hz, J = 2.2 Hz, aromat.), 8.00 (td, 1H, J = 8.1 Hz, J = 2.0 Hz, aromat.), 8.34 (dd, 1H, J = 4.7 Hz, J = 1.7 Hz, aromat.), 8.92 (d, 1H, J = 1.6 Hz, aromat.), 10.35 (s, 1H). CI-MS (NH_3) *m/z* (%): 398 (100) $[M + H^+]^+$. Anal. ($C_{24}H_{23}N_5O \cdot 1/3H_2O$): C, H, N.

*6.4.24. N-(4-Ethyl-3-(4-(pyridin-3-yl)-1H-imidazol-2-ylamino)phenyl)-4-methylbenzamide (**11e**)*

Yield: 0.41 g (51%), white crystals, mp: 150.4–150.6 °C. IR (KBr): ν (cm^{-1}) = 3436, 2965, 1669, 1611. ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.08 (t, 3H, J = 7.5 Hz), 2.39 (s, 3H), 2.44 (q, br., 2H, J = 6.9 Hz), 5.47 (s, 2H), 7.30–7.37 (m, 3H, aromat.), 7.41 (d, 2H, J = 8.9 Hz, aromat.), 7.80 (d, 1H, J = 2.2 Hz, aromat.), 7.89 (d, 3H, J = 8.2 Hz, aromat.), 8.00 (td, 1H, J = 8.0 Hz, J = 2.0 Hz, aromat.), 8.34 (dd, 1H, J = 4.8 Hz, J = 1.5 Hz, aromat.), 8.92 (d, 1H, J = 1.9 Hz, aromat.), 10.31 (s, 1H). CI-MS (NH_3) *m/z* (%): 398 (100) $[M + H^+]^+$. Anal. ($C_{24}H_{23}N_5O$): C, H, N.

*6.4.25. N-(4-Methyl-3-(4-(pyridin-4-yl)-1H-imidazol-2-ylamino)phenyl)benzamide (**12b**)*

Yield: 0.36 g (65%), yellow crystals, mp: 248.9–251.1 °C. IR (KBr): ν (cm^{-1}) = 3423, 1640, 1604. ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.11 (s, 3H), 5.56 (s, 2H), 7.40 (d, 1H, J = 9.1 Hz, aromat.), 7.51–7.68 (m, 6H, aromat.), 7.81–7.86 (m, 2H, aromat.), 7.95 (dd, 2H, J = 1.4 Hz, J = 8.1 Hz, aromat.), 8.45 (dd, 2H, J = 1.5 Hz, J = 4.6 Hz, aromat.), 10.39 (s, 1H). PI-EIMS (70 eV) *m/z* (%): 369 (100) $[M]^{+\bullet}$, 105 (78), 77 (51). Anal. ($C_{22}H_{19}N_5O \cdot 1/2H_2O$): C, H, N.

*6.4.26. N-(4-Methyl-3-(4-(pyridin-4-yl)-1H-imidazol-2-ylamino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (**12l**)*

Yield: 0.22 g (47%), mp: 256.6–256.7 °C. IR (KBr): ν (cm^{-1}) = 3402, 2941, 2800, 1647. ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.10 (s, 3H), 2.16 (s, 3H), 2.35 (s, br., 8H), 3.53 (s, 2H), 5.55 (s, 2H, exchangeable), 7.37–7.40 (m, 1H, aromat.), 7.43–7.46 (m, 2H, aromat.), 7.55 (s, 1H, aromat.),

7.60–7.62 (AA′, 2H, aromat.), 7.80–7.84 (m, 2H, aromat.), 7.89–7.91 (BB′, 2H, aromat.), 8.44–8.46 (BB′, 2H, aromat.), 10.35 (s, 1H, exchangeable). EI-MS (70 eV) *m/z* (%): 481 (31) $[M]^{+\bullet}$, 466 (18), 425 (27), 411 (88), 383 (100), 118 (23), 99 (20), 90 (18). Anal. ($C_{28}H_{31}N_7O \cdot 1/2H_2O$): C, H, N.

Appendix. Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.ejmech.2007.09.021.

References

[1] J. Dancey, E.A. Sausville, Nat. Rev. Drug Discov. 2 (2003) 296–313.
[2] K. Pietras, T. Sjoblom, K. Rubin, C.H. Heldin, A. Ostman, Cancer Cell 3 (2003) 439–443.
[3] A. Ostman, C.H. Heldin, Adv. Cancer Res. 97 (2007) 247–274.
[4] C.H. Heldin, A. Ostman, L. Ronnstrand, Biochim. Biophys. Acta 1378 (1998) 79–113.
[5] J. Zimmermann, E. Buchdunger, H. Mett, T. Meyer, N.B. Lydon, B. Nicholas, P. Traxler, Bioorg. Med. Chem. Lett. 6 (1996) 1221–1226.
[6] E. Buchdunger, C.L. Cioffi, N. Law, D. Stover, S. Ohno-Jones, B.J. Druker, N.B. Lydon, J. Pharmacol. Exp. Ther. 295 (2000) 139–145.
[7] J. Zimmermann, E. Buchdunger, H. Mett, T. Meyer, N.B. Lydon, Bioorg. Med. Chem. Lett. 7 (1997) 187–192.
[8] E. Buchdunger, T. O'Reilly, J. Wood, Eur. J. Cancer 38 (Suppl. 5) (2002) 28–36.
[9] R. Capdeville, E. Buchdunger, J. Zimmermann, A. Matter, Nat. Rev. Drug Discov. 1 (2002) 493–502.
[10] M. Deininger, E. Buchdunger, B.J. Druker, Blood 105 (2005) 2640–2653.
[11] M. Ciufolini, A. Benjahad, B. Giethlen, A. Moussy, C. Wermuth, PCT Int. Appl., WO 2006/064375 A2, 2006.
[12] A. Dornow, H. Machens, K. Bruncken, Chem. Ber. 84 (1951) 147–150.
[13] E. Vanotti, R. D'Alessio, M. Tibolla, M. Varasi, A. Montagnoli, C. Santocanale, K. Martina, M. Menichincheri, PCT Int. Appl., WO 2005013986 A1, 2005.
[14] S. Wang, G. Wood, C. Meades, G. Griffiths, C. Midgley, I. McNae, C. McInnes, S. Anderson, W. Jackson, M. Mezna, R. Yuill, M. Walkinshaw, P.M. Fischer, Bioorg. Med. Chem. Lett. 14 (2004) 4237–4240.
[15] Z. Szakacs, S. Beni, Z. Varga, L. Oerfi, G. Keri, B. Noszla, J. Med. Chem. 48 (2005) 249–255.
[16] S. Mahboobi, A. Sellmer, T. Burgemeister, A. Lyssenko, D. Schollmeyer, Monatsh. Chem. 135 (2004) 333–342.
[17] M. Sattler, S. Verma, C.H. Byrne, G. Shrikhande, T. Winkler, P.A. Algate, L.R. Rohrschneider, J.D. Griffin, Mol. Cell. Biol. 19 (1999) 7473–7480.
[18] F.D. Böhmer, L. Karagyozov, A. Uecker, H. Serve, A. Botzki, S. Mahboobi, S. Dove, J. Biol. Chem. 278 (2003) 5148–5155.
[19] S. Mahboobi, A. Uecker, A. Sellmer, C. Cénac, H. Höcher, H. Pongratz, E. Eichhorn, H. Hufsky, A. Trümpler, M. Sicker, F. Heidel, T. Fischer, C. Stocking, S. Elz, F.-D. Böhmer, S. Dove, J. Med. Chem. 49 (2006) 3101–3115.
[20] S. Mahboobi, S. Teller, H. Pongratz, H. Hufsky, A. Sellmer, A. Botzki, A. Uecker, T. Beckers, S. Baasner, C. Schachtele, F. Ueberall, M.U. Kassack, S. Dove, F.-D. Böhmer, J. Med. Chem. 45 (2002) 1002–1018.