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# Synthesis of Imidazo[2,1-*a*]phthalazines, Potential Inhibitors of p38 MAP Kinase. Prediction of Binding Affinities of Protein Ligands

Based upon molecular modeling, the pharmacophore of potential inhibitors of p38 MAPK (mitogen-activated protein kinases) is discussed and the predictive binding affinities are calculated. Syntheses of original diarylimidazo[2,1-*a*]phthalazines obtained by Suzuki coupling are described.

**Keywords:** Imidazophthalazine; Suzuki coupling; Molecular modeling; p38 MAPK

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## Introduction

Mitogen-activated protein (MAP) kinases are important signaling molecules. They participate in diverse cellular events and are potential targets for intervention in inflammation, arthritis and other joint diseases, septic shock and myocardial injury [1]. Activation of p38 MAP kinase results in the production of IL-1 and TNF-α, suggesting that inhibition of this kinase may provide a useful therapeutic target for intervention in various diseases mediated by these cytokines [2, 3].

The rapid and accurate calculation of binding free energy of putative protein-ligand complexes is difficult to evaluate but important to consider in the structure-based drug design. The LUDI program (MSI/Byosim, San Diego, USA) has a simple scoring function to predict binding constants for protein-ligand complexes of known three-dimensional structure [4–7]. The LUDI program positions molecular fragments or small molecules into protein binding sites in such a way that hydrogen bonds are formed with the protein, and lipophilic groups are placed into hydrophobic pockets. Ionic interactions and the number of rotatable bonds in the ligand are also taken into account. It was shown that a very significant correlation between the sum of atom pair potentials and total binding free energy exists, and the sum is therefore a good measure for estimating binding affinities [8]. It was demonstrated for a great number of structures that the LUDI predictive function is quite a good model for nanomolar to 100 nM activities [9].

Different pyridinylimidazole compounds, such as SB203580, were found to be selective inhibitors of p38 MAP kinase [10, 11]. These compounds have effects on eicosanoid production, consistently inhibiting IL-1 and TNF synthesis in human monocytes at concentrations in the low μM range [2]. X-ray crystallographic studies showed that pyridinylimidazole interacts with the ATP binding pocket. The pyridyl nitrogen mimics the N-1 nitrogen of the adenine ring of ATP.

In continuing our interest in the investigation of bi- and tricyclic hetero compounds, the influences of the tricyclic system pyridinylimidazole on the inhibition of p38 MAP kinase were studied. Only few 2-phenylimidazo[2,1-*a*]phthalazines are reported in the literature [12, 13], and were designed as CNS agents. To the best of our knowledge, no 2,3-diaryl compounds have been described. In the light of our experience, imidazo[2,1-*a*]phthalazine compounds have been prepared by our general method previously described in the imidazopyridine series [14].

## Results

The 2-arylimidazophthalazines **4a**–**c** were prepared in good yield from aminophthalazine by reaction with phenacyl bromide or *p*-fluorophenacyl bromide in refluxing ethanol (Scheme 1). Iodination of **4a**–**c** with *N*-iodosuccinimide in acetonitrile at room temperature, according to the procedure described in the imidazo[1,2-*a*]pyridine series [15], gave the 3-iodo derivatives in good yield. Treatment of iodoimidazophthalazine **5a**–**c** by Pd(0)-catalyzed cross coupling with aryl- or heteroarylboronic acid under Suzuki condition [16, 17] yielded diarylimidazophthalazine **6a**–**h**. Benzene, 4-fluorobenzene and 3-pyridyl boronic acids were used as well as pyridine-3-boronic acid 1,3-propanediol cyclic ester. For this last-mentioned compound, under the same reaction conditions, yields were equivalent. The imidazophthalazine structures are listed in Table 1.

## Discussion

Four distinct members of the p38 MAPK family have been identified to date, standardized in the nomenclature as p38α, β, χ and δ. These kinases are 60 to 70% identical to each other [19, 20]. Thus, the X-ray crystallo-

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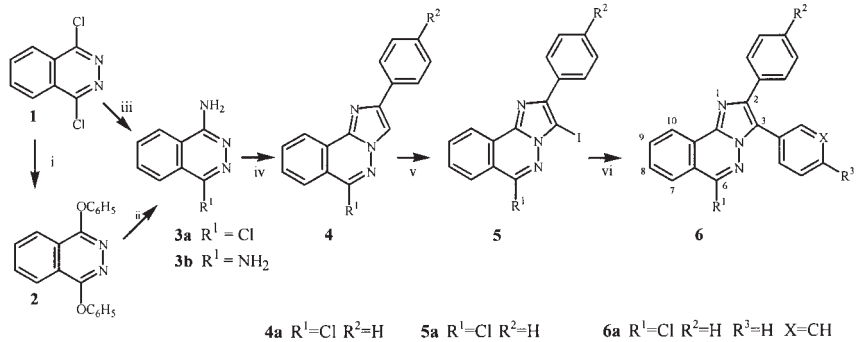


**4a** $R^1$=Cl $R^2$=H **5a** $R^1$=Cl $R^2$=H **6a** $R^1$=Cl $R^2$=H $R^3$=H X=CH

**4b** $R^1$=Cl $R^2$=F **5b** $R^1$=Cl $R^2$=F **6b** $R^1$=Cl $R^2$=H $R^3$=F X=CH

**4c** $R^1$=$NH_2$ $R^2$=H **5c** $R^1$=$NH_2$ $R^2$=H **6c** $R^1$=Cl $R^2$=H $R^3$=H X=N

**6d** $R^1$=Cl $R^2$=F $R^3$=H X=CH

**6e** $R^1$=Cl $R^2$=F $R^3$=F X=CH

**6f** $R^1$=Cl $R^2$=F $R^3$=H X=N

**6g** $R^1$=$NH_2$ $R^2$=H $R^3$=H X=CH

**6h** $R^1$=$NH_2$ $R^2$=H $R^3$=F X=CH

**6i** $R^1$=$NH_2$ $R^2$=H $R^3$=H X=N

**Scheme 1.** (a) *Reaction condition:* (i): KOH, phenol, 100 °C, 2 h; (ii) for **3b**: $CH_3CO_2NH_4$, 160 °C, 1 h; (iii) for **3a**: $NH_4OH$, Parr apparatus, 120 °C, 4 h; (iv): phenacyl bromide or fluorophenacyl bromide, EtOH, reflux, 4 h; (v): *N*-iodosuccinimide, acetonitrile, room temperature, 45 min; (vi): $Pd(PPh_3)_4$, aryl- or heteroarylboronic acid, DME, NaOH, $H_2O$, reflux, 8 h.

**Table 1.** Physical data for compounds **4**, **5**, **6**.

| | $R^1$ | $R^2$ | $R^3$ | X | Yield [%] | Mp [°C] | Formula | Analysis Calcd./found [%] C, H, N |
|---|---|---|---|---|---|---|---|---|
| **4a** | Cl | H | – | – | 81 | 156–158 | $C_{16}H_{10}ClN_3$ | 68.70, 3.60, 15.02<br>68.98, 3.61, 15.01 |
| **4b** | Cl | F | – | – | 75 | 236–238 | $C_{16}H_9ClFN_3$ | 64.55, 3.05, 14.11<br>64.65, 3.06, 14.09 |
| **4c** | $NH_2$ | H | – | – | 68 | 210–212[a] | $C_{16}H_{12}N_4$ | 73.83, 4.65, 21.52<br>73.99, 4.65, 21.60 |
| **5a** | Cl | H | – | – | 67 | 190–192 | $C_{16}H_9ClIN_3$ | 47.38, 2.24, 10.36<br>47.58, 2.25, 10.32 |
| **5b** | Cl | F | – | – | 68 | 206–208 | $C_{16}H_8ClFIN_3$ | 45.37, 1.90, 9.92<br>45.57, 1.90, 9.90 |
| **5c** | $NH_2$ | H | – | – | 60 | 194–196 | $C_{16}H_{11}IN_4$ | 49.76, 2.87, 14.51<br>49.95, 2.88, 14.49 |

**Table 1.** (continued)

| | $R^1$ | $R^2$ | $R^3$ | X | Yield [%] | Mp [°C] | Formula | Analysis Calcd./found [%] C, H, N |
|---|---|---|---|---|---|---|---|---|
| **6a** | Cl | H | H | CH | 63 | 218–220 | $C_{22}H_{14}ClN_3$, $H_2O$ | 70.68, 4.31, 11.24<br>70.75, 4.30, 11.25 |
| **6b** | Cl | H | F | CH | 51 | 216–218 | $C_{22}H_{13}ClFN_3$ | 70.69, 3.51, 11.24<br>70.69, 3.53, 11.21 |
| **6c** | Cl | H | H | N | 46 | 220–224 | $C_{21}H_{13}ClN_4$, $H_2O$ | 67.29, 4.03, 14.95<br>67.15, 4.03, 14.89 |
| **6d** | Cl | F | H | CH | 61 | 168–170 | $C_{22}H_{13}ClFN_3$ | 70.69, 3.51, 11.24<br>70.49, 3.52, 11.23 |
| **6e** | Cl | F | F | CH | 43 | 220–222 | $C_{22}H_{12}ClF_2N_3$ | 67.44, 3.09, 10.72<br>67.14, 3.11, 10.71 |
| **6f** | Cl | F | H | N | 49 | 222–224 | $C_{21}H_{12}ClFN_4$ | 67.30, 3.23, 14.95<br>66.98, 3.24, 14.93 |
| **6g** | $NH_2$ | H | H | CH | 48 | 250–252 | $C_{22}H_{16}N_4$ | 78.55, 4.79, 16.66<br>78.26, 4.79, 16.70 |
| **6h** | $NH_2$ | H | F | CH | 53 | 234–236 | $C_{22}H_{15}FN_4$ | 74.56, 4.27, 15.81<br>74.21, 4.28, 15.81 |
| **6i** | $NH_2$ | H | H | N | 49 | 156–158 | $C_{22}H_{15}N_5$, $H_2O$ | 70.97, 4.82, 19.71<br>71.18, 4.81, 19.70 |

[a] in the literature 215–216 °C [12].

graphic structures of native unactivated p38α (unphosphorylated form), or the pyrimidinylimidazole p38 complex were used for the molecular modeling studies [20, 21]. It was demonstrated that the arylpyridinylimidazole structures bind in the same site on the kinase, as does ATP [22, 23]. Biochemical studies combined with enzyme mutagenesis support this model [24]. The structural relevance of the inactivated form of p38 to the phosphorylated active form is not known, although members of the pyridinylimidazole class of inhibitors, which compete with ATP, have similar affinity for the active and inactive form of the enzyme [25, 26]. The p38-binding site is formed by Val38, Val52, Lys53, Glu71, Leu75, Ile84, Leu104, Thr106, and Asp168 [20, 22, 23]. Mutagenesis showed that a single residue difference between p38 MAPK and other MAPK is sufficient to confer selectivity among pyridinylimidazole compounds [19, 23, 26]. The p38 kinase inhibitors contain a common set of structural features. A pharmacophore derived from a series of several tri- and tetra-substituted imidazole inhibitors of p38 has been described by Gallagher et al. [27]. In general, the inhibitors contain a 4-aryl-5-pyridinylimidazole structure [20, 21]. The 4-pyridyl substituent has been shown to be essential for activity.

Further substitution of the imidazole at N-1 adjacent to the pyridinyl group or at the C-2 is allowed, while substitution of the imidazole nitrogen adjacent to the aryl group is not [27]. The structure-activity relationships (SAR) have been described with pyrrole [26] and pyrazolinone triaryl substituents, suggesting a similar binding mode. Optimization of binding occurs with pyrrole substituents. Substituted pyrimidines as replacement for the 4-pyridinyl group have demonstrated improved activity [28]. In attempt to develop a ligand-binding model for inhibition of p38 enzyme, the LUDI scoring program was used to identify which compounds could fit into this enzyme's active site. We investigated, by the LUDI program, binding interactions of the different **6a**–**e** imidazophthalazine in the ATP pocket of p38 and calculated the empirical binding affinities at physiological pH. To have a comparative level, we studied some diaryl imidazole **Ia**–**e** (Table 4) inhibitors of p38 MAP kinase described by Liverton et al. [29]. The binding affinities $K_i$ are only a predictive value, with an error range of about 1–4 log $K_i$ units. In our

**Table 2.** $^1$H-NMR data for compounds **4**, **5**, **6**: δ (ppm).

| | H(3) | H(7) | H(8) | H(9) | H(10) | Others |
|---|---|---|---|---|---|---|
| **4a**[a] | 8.08 | 8.15 | 7.68 | 7.88 | 8.63 | 7.42 (3 $H_{arom}$), 8.00 (2 $H_{arom}$) |
| **4b**[a] | 8.27 | 8.54 | 7.92 | 8.27 | 8.76 | 7.33 (2 $H_{arom}$), 8.10 (2 $H_{arom}$) |
| **4c**[b] | 8.28 | 8.28 | 7.72 | 7.90 | 8.38 | 6.90 ($NH_2$), 7.25 (1 $H_{arom}$), 7.43 (2 $H_{arom}$), 7.90 (2 $H_{arom}$) |
| **5a**[a] | – | 8.29 | 7.92 | 7.99 | 8.70 | 7.52 (3 $H_{arom}$), 8.20 (2 $H_{arom}$) |
| **5b**[a] | – | 8.18 | 7.82 | 7.99 | 8.66 | 7.23 (2 $H_{arom}$), 8.26 (2 $H_{arom}$) |
| **5c**[b] | – | 8.31 | 7.74 | 7.92 | 8.41 | 7.21 ($NH_2$), 7.35 (1 $H_{arom}$), 7.50 (2 $H_{arom}$), 8.12 (2 $H_{arom}$) |
| **6a**[a] | – | 8.24 | 7.78 | 7.97 | 8.75 | 7.39 (3 $H_{arom}$), 7.54 (3 $H_{arom}$), 7.65 (2 $H_{arom}$), 7.78 (2 $H_{arom}$) |
| **6b**[a] | – | 8.26 | 7.98 | 7.80 | 8.76 | 7.23 (2 $H_{arom}$), 7.36 (3 $H_{arom}$), 7.63 (2 $H_{arom}$), 7.73 (2 $H_{arom}$) |
| **6c**[a] | – | 8.28 | 7.76 | 7.92 | 8.80 | 7.57 (4 $H_{arom}$), 7.92 (1 $H_{arom}$), 8.13 (1 $H_{arom}$), 8.28 (1 $H_{arom}$), 8.88 (1 $H_{arom}$), 9.05 (1 $H_{arom}$) |
| **6d**[a] | – | 8.23 | 7.77 | 7.96 | 8.73 | 7.63 (7 $H_{arom}$), 7.07 (2 $H_{arom}$) |
| **6e**[a] | – | 8.23 | 7.74 | 7.68 | 8.70 | 7.07 (2 $H_{arom}$), 7.23 (2 $H_{arom}$), 7.65 (4 $H_{arom}$) |
| **6f**[a] | – | 8.28 | 7.82 | 7.38 | 8.73 | 7.10 (2 $H_{arom}$), 7.48 (1 $H_{arom}$), 7.67 (2 $H_{arom}$), 8.00 (1 $H_{arom}$), 8.73 (1 $H_{arom}$), 8.87 (1 $H_{arom}$) |
| **6g**[b] | – | 8.26 | 7.75 | 7.92 | 8.46 | 6.87 ($NH_2$), 7.30 (3 $H_{arom}$), 7.52 (7 $H_{arom}$) |
| **6h**[a] | – | 8.38 | 7.77 | 7.96 | 8.72 | 6.93 (2 $H_{arom}$), 7.40 ($NH_2$, 5 $H_{arom}$), 7.74 (2 $H_{arom}$) |
| **6i**[a] | – | 8.37 | 7.73 | 7.95 | 8.70 | 7.15 (1 $H_{arom}$), 7.36 ($NH_2$, 4 $H_{arom}$), 7.72 (3 $H_{arom}$), 8.48 (1 $H_{arom}$), 8.66 (1 $H_{arom}$) |

[a] solvent: $CDCl_3$, [b] solvent: DMSO-$d_6$.

studies, for the structures **Ia**–**e**, with a supposed $K_i \cong IC_{50}/2$, a difference of 1.5 log $K_i$ units was found. This is the reason why the $IC_{50}$ values are given in nM when the predictive $K_i$ are in µM, but it permits arrangement of the values in order of size and enables comparison with the different structures. The predictive activity for **6c** falls into the range of experimental values reported in the imidazole series (between 50 and 150 nM). For **6f**, **g**, **i** and **6b**, $IC_{50}$ might be between 0.5 and 1 µM. "No score" means that the LUDI program failed to place the structure into the ATP pocket (corresponding to poor activity as for **Ie** with a $IC_{50}$ > 10,000 nM). The imidazophthalazine skeleton seemed to be an excellent structure for the inhibition of p38 MAPK, and a 3-pyridin-3-yl substituent led to a predictive $K_i$ < 20 µM. The importance of a fluorine atom on the aryl ring at C(2) could not be demonstrated (no score for **6d** and **6e**). Substitution at C(6) on the phthalazine system by a chlorine atom or an amino group does not contribute significantly to activity.

The binding interactions defined by the docked structures (Figure 1) are in good agreement with these described by X-ray crystallographic studies of the pyridinylimidazole inhibitor [20–23] or in the quinazoline class [30]:

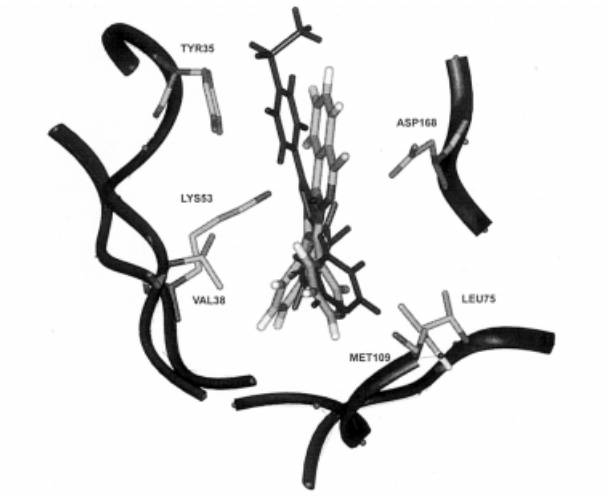



**Fig. 1.** ATP pocket of p38 with residues which bind, in predictive studies, with **Ia** (in black) and **6c** (in gray). Lys53 and Met109 gave hydrogen bonds, Tyr35, Val38, Leu75, Ile84, and Asp168 formed the aryl binding pocket.

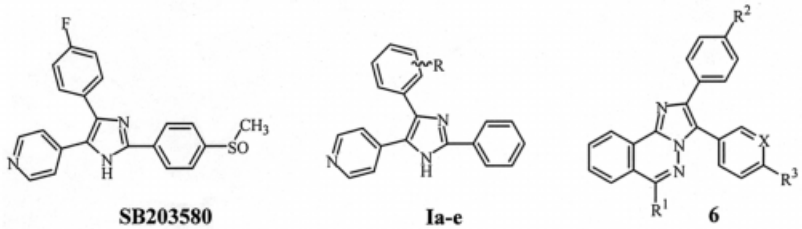
**Table 3.** $^{13}$C-NMR for compounds **4**, **5**, **6**: δ (ppm), *J* (Hz).

| | C(2) | C(3) | C(6) | C(6a) | C(7) | C(8) | C(9) | C(10) | C(10a) | C(10b) | Others |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **4a**[a] | 143.0 | 112.8 | 146.9 | 125.9 | 126.7 | 129.1 | 133.5 | 122.8 | 121.6 | 136.2 | 125.7, 127.9, 128.7, 133.2 |
| **4b**[b] | 142.2 | 112.6 | 147.2 | 126.0 | 126.9 | 129.3 | 133.8 | 121.8 | 121.8 | 136.4 | 115.7 (*J* = 21), 127.4 (*J* = 8), 129.5 (*J* = 3), 162.7 (*J* = 249) |
| **4c**[b] | 140.4 | 113.5 | 153.1 | 117.9 | 125.3 | 128.8 | 133.0 | 122.4 | 126.2 | 134.9 | 125.3, 128.8, 129.0, 135.1 |
| **5a**[a] | 147.8 | 98.2 | 140.1 | 125.8 | 127.0 | 129.6 | 133.9 | 122.4 | 121.9 | 136.6 | 128.5, 127.5, 128.3, 132.6 |
| **5b**[a] | 139.3 | 97.8 | 146.5 | 125.8 | 127.1 | 129.8 | 134.0 | 122.4 | 122.0 | 137.7 | 115.5 (*J* = 21), 128.1 (*J* = 3), 129.3 (*J* = 8), 162.5 (*J* = 248) |
| **5c**[b] | 141.7 | 95.3 | 153.2 | 118.0 | 125.2 | 129.1 | 133.0 | 121.9 | 125.7 | 134.6 | 127.5, 127.6, 128.6, 137.2 |
| **6a**[a] | 140.2 | 125.1 | 146.8 | 121.8 | 126.9 | 129.1 | 133.5 | 122.9 | 125.8 | 135.7* | 127.6, 128.2, 128.4, 128.6, 130.6, 133.5* |
| **6b**[a] | 140.4 | 124.6 | 146.9 | 121.9 | 126.8 | 129.3 | 133.7 | 123.0 | 126.3 | 135.8 | 115.8 (*J* = 21), 124.6 (*J* = 3), 127.7, 128.2, 128.5, 133.8 (*J* = 8), 133.9, 162.8 (*J* = 249) |
| **6c**[a] | 140.4 | 125.4 | 152.1 | 122.2 | 127.7 | 129.2 | 133.1 | 122.6 | 125.9 | 137.4 | 123.5, 127.7, 128.2, 128.5, 131.1, 133.0, 137.4, 150.5, 150.8 |
| **6d**[a] | 139.4 | 125.4 | 146.9 | 121.9 | 126.9 | 129.3 | 133.7 | 122.9 | 126.3 | 135.7, | 115.4 (*J* = 21), 128.3, 128.7, 128.7, 129.9 (*J* = 8), 130.2 (*J* = 3), 130.6, 162.5 (*J* = 247) |
| **6e**[a] | 139.4 | 124.4 | 147.0 | 121.9 | 126.9 | 129.3 | 133.7 | 122.9 | 126.2 | 135.8, | 115.4 (*J* = 21), 115.9 (*J* = 21), 124.3 (*J* = 3), 128.3, 130.0 (*J* = 8), 130.1 (*J* = 3), 132.4 (*J* = 8), 162.5 (*J* = 248), 162.9 (*J* = 248) |
| **6f**[a] | 140.5 | 124.9 | 147.3 | 122.1 | 127.0 | 129.6 | 133.9 | 123.0 | 126.1 | 136.4 | 115.7 (*J* = 21), 123.5, 129.7, 130.0 (*J* = 8), 137.6, 130.1, 149.4, 151.0, 162.7 (*J* = 234) |
| **6g**[b] | 137.4 | 124.9 | 152.6 | 117.8 | 125.0 | 128.7 | 132.8 | 122.3 | 126.0 | 130.2 | 127.0, 127.3, 128.5, 128.9, 131.1, 134.3, 135.1 |
| **6h**[a] | 139.7 | 124.3 | 153.2 | 117.7 | 124.7 | 128.7 | 133.3 | 122.8 | 127.2 | 134.7* | 115.0 (*J* = 21), 121.5, 124.7 (*J* = 3), 127.4, 128.4 (*J* = 7), 129.4, 135.4*, 162.2 (*J* = 248) |
| **6i**[a] | 140.6 | 122.0 | 152.9 | 117.8 | 124.6 | 128.9 | 133.3 | 122.8 | 125.2 | 134.2* | 121.4, 122.6, 127.0, 127.7, 128.8, 135.9*, 136.9, 148.3, 150.4 |

[a] solvent: $CDCl_3$, [b]: solvent: DMSO-$d_6$.

– A hydrogen bond between the 3-pyridyl nitrogen (for **6c**, **6f**, **6i**) and the amide N-H of Met109 (a hydrogen bond between the 4-pyridyl nitrogen for SB203580 and Met109) with a N-NH (Met109) distance of 2.2 Å. It is analogous to the H bond which is seen for the N-1 adenine of ATP in all available kinase crystal structures.
– H-bond-like interaction between Lys53 and the nitrogen N(1) for **6c**, **6f**, **6g**, **6i**.
(H-bond-like interaction between Lys53 and the unalkylated imidazole N-H with SB203580)
– Potential H-bond-like interaction with Asp168 (with **6g**)

**Table 4.** p38 inhibition data for literature compounds [30] and predictive binding of complex p38-ligand.



SB203580 Ia-e 6

| Compd $R^1$ | R or $R^2$ $R^3$ | $IC_{50}$ [nM][a] | $K_i$ pred[b] [μM] pH=7.4 |
|---|---|---|---|
| **Ia** | R = 3,4-$Cl_2$ | 28 | 6 |
| **Ib** | R = 4-Cl | 48 | 9 |
| **Ic** | R = H | 180 | 25 |
| **Id** | R = 3-F | 495 | 21 |
| **Ie** | R = 4-$CO_2CH_3$ | >10000 | -[c] |
| **6a** $R^1$=Cl | $R^2$ = H $R^3$ = H | ND | - |
| **6b** $R^1$=Cl | $R^2$ = H $R^3$ = F | ND | 107 |
| **6c** $R^1$=Cl | $R^2$ = H X = N, $R^3$ = H | ND | 19 |
| **6d** $R^1$=Cl | $R^2$ = F $R^3$ = H | ND | - |
| **6e** $R^1$=Cl | $R^2$ = F $R^3$ = F | ND | - |
| **6f** $R^1$=Cl | $R^2$ = F X = N, $R^3$ = H | ND | 31 |
| **6g** $R^1$= $NH_2$ | $R^2$ = H $R^3$ = H | ND | 40 |
| **6h** $R^1$=$NH_2$ | $R^2$ = H $R^3$ = F | ND | - |
| **6i** $R^1$= $NH_2$ | $R^2$ = H X = N, $R^3$ = H | ND | 57 |

[a] Literature inhibitory concentration in nM required to inhibit 50% of p38 MAPK. [b] Predictive $K_i$ (score = –100 log $K_i$). [c] "-"means "no score". ND: not determined yet.

– Hydrophobic contacts between potent inhibitor and Val38 (with **6g**), Tyr35 (with **6b**), Leu75 (with **6b**), Ile84 (with **6b**). The distances between the potent inhibitor and the enzyme are all within 4 Å.

In conclusion, we have prepared in an efficient way new 2,3-diarylimidazo[2,1-*a*]phthalazine derivatives which, in their conception, are of great potential biological interest as inhibitors of p38 MAP kinase. Biological evaluation will be performed in order to confirm the model obtained by molecular modeling studies.

## Experimental Section

All melting points were determined on a Kofler hot-plate melting point apparatus and were uncorrected. $^1$H and $^{13}$C-NMR spectra were recorded on a Bruker DPX-200 spectrometer (SAVIT, Tours, France). Elemental analysis were performed by Microanalytical Center, ENSCM, Montpellier, France.

Compounds **2**, **3a** and **3b** were prepared following reported methods [31–33]. The structure of all the new compounds was determined using $^1$H (Table 2) and $^{13}$C-NMR (Table 3) spectroscopy and when necessary by $^{13}$C-$^1$H correlation (XHCOR) and long-range $^{13}$C-$^1$H correlation (LRHETCOR).

*6-Chloro-2-arylimidazo[2,1-a]phthalazine* **4a,b** *and 6-amino-2-arylimidazo[2,1-a]phthalazine* **4c**

A solution of aminophthalazine **3a**–**c** (10 mmol) and 2′-bromoacetophenone (or 2′-bromo-4-fluoroacetophenone, or 2′-bromopyridyn-3-ylethanone) (9 mmol) was heated under reflux in ethanol (20 mL) for 4 h. After cooling, the solution was concentrated, the precipitate was filtered and washed with diethyl ether. The crude product was separated by flash chromatography on silica gel, eluted with ethyl acetate/hexane (5/5 v/v) to give **4a**–**c**.

*6-Chloro-3-iodo-2-arylimidazo[2,1-a]phthalazine* **5a,b** *and 6-amino-3-iodo-2-arylimidazo[2,1-a]phthalazine* **5c**

*N*-Iodosuccinimide (2.2 mmol) was added to a solution of imidazophthalazine **4a**–**c** (2 mmol) in 5 mL acetonitrile. The resulting mixture was stirred at room temperature for 45 min. The pre-

cipitate formed was filtered and washed with acetonitrile. The crude product was purified chromatographically on a silica gel column and eluted with ethyl acetate/hexane (10/90 v/v) to give **5a**–**c**.

*Palladium catalyst*

Tetrakis(triphenylphosphine)palladium(0) was prepared according to the procedure of Coulson [34].

*6-Chloro-2,3-diarylimidazo[2,1-a]phthalazine* **6a**–**f** *and 6-amino-2,3-diarylimidazo[2,1-a]phthalazine* **6g**–**i**

To a mixture of 3-iodoimidazophtalazine **5a**–**c** (0.5 mmol) in 4 mL dimethoxyethane (DME), under nitrogen, Pd(PPh3)4 (0.025 mmol), aryl boronic acid or pyridine-3-boronic acid 1,3-propanediol cyclic ester (0.55 mmol), and 2 mL of 4 N aqueous sodium hydroxide solution were added. The reaction mixture was heated under reflux for 8 h. After cooling, the mixture was poured into a brine solution (100 mL) and then extracted with dichloromethane. The organic layers were dried over anhydrous magnesium sulfate and evaporated to dryness under vacuo. The crude product was separated by chromatography on a flash silica gel column and eluted with dichloromethane/hexane (30/70, v/v) to give **6a**–**i**.

*Molecular modeling*

The calculations and simulations were performed on an Indigo 2 SGI workstation using the software modules Builder, Ampac/Mopac, Homology and LUDI in the MSI/Biosym package (vers. insightII 98.0). The structure of the p38 enzyme comes from the Protein Data Bank. Hydrogen atoms were added automatically using the Builder module with the pH set to the physiological value of 7.4. Local minimum conformers of evaluated structures were obtained by full energy minimization using AM1 calculation with Mopac hessian.

The coordinate of the centroid of the inhibitor SB203580 in the protein-ligand complex (1A9U)a [20] was taken as the center of the investigation in the p38 enzyme (1P38)[a]. The rms deviation between these two proteins evaluated by the homology module was 0.387 Å. Interaction sites were calculated within a radius of 6.0 Å of several points in this region. The fit was achieved with a maximum rms deviation of 0.6 Å from the interaction sites for the structure.

[a] access four-character code in Brookhaven Protein Databank (PDB).

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