



Discovery of chromenes as inhibitors of macrophage migration inhibitory factor

Tjie Kok^{a,e,f}, Hannah Wapenaar^{a,f}, Kan Wang^{b,f}, Constantinos G. Neochoritis^{b,f}, Tryfon Zarganes-Tzitzikas^b, Giordano Proietti^a, Nikolaos Eleftheriadis^{a,c}, Katarzyna Kurpiewska^d, Justyna Kalinowska-Tłuścik^d, Robbert H. Cool^a, Gerrit J. Poelarends^a, Alexander Dömling^b, Frank J. Dekker^{a,*}

^a Department of Chemical and Pharmaceutical Biology, University of Groningen, Groningen, The Netherlands

^b Department of Drug Design, University of Groningen, Groningen, The Netherlands

^c Molecular Microscopy Research Group, Zernike Institute for Advanced Materials, University of Groningen, Groningen, The Netherlands

^d Faculty of Chemistry, Jagiellonian University, 3 Ingardena Street, 30-060 Kraków, Poland

^e Faculty of Biotechnology, University of Surabaya, Jalan Raya Kalirungkut, Surabaya 60292, Indonesia

ARTICLE INFO

Article history:

Received 16 November 2017

Revised 20 December 2017

Accepted 22 December 2017

Available online 24 December 2017

Keywords:

Macrophage migration inhibitory factor

Chromenes

Inhibitor

Enzyme kinetics

ABSTRACT

Macrophage migration inhibitory factor (MIF) is an essential signaling cytokine with a key role in the immune system. Binding of MIF to its molecular targets such as, among others, the cluster of differentiation 74 (CD74) receptor plays a key role in inflammatory diseases and cancer. Therefore, the identification of MIF binding compounds gained importance in drug discovery. In this study, we aim to discover novel MIF binding compounds by screening of a focused compound collection for inhibition of its tautomerase enzyme activity. Inspired by the known chromen-4-one inhibitor Orita-13, a focused collection of compounds with a chromene scaffold was screened for MIF binding. The library was synthesized using versatile cyanoacetamide chemistry to provide diversely substituted chromenes. The screening provided inhibitors with IC₅₀'s in the low micromolar range. Kinetic evaluation suggested that the inhibitors were reversible and did not bind in the binding pocket of the substrate. Thus, we discovered novel inhibitors of the MIF tautomerase activity, which may ultimately support the development of novel therapeutic agents against diseases in which MIF is involved.

© 2017 Elsevier Ltd. All rights reserved.

1. Introduction

Macrophage migration inhibitory factor (MIF) is a central cytokine of the immune system. It is expressed in immune cells such as T-cells, macrophages, basophiles, eosinophils and B-cells.¹ Unlike other cytokines, MIF is constitutively expressed and stored in cytoplasmic pools and rapidly released in response to stimuli.² Upon release, MIF interacts with surface receptors on B-cells, T-cells, macrophages and some epithelial cells, which induce pro-inflammatory signal transduction. MIF has been shown to interact with the type II cluster of differentiation 74 (CD74) receptor, which is the invariant chain of the major histocompatibility complex II (MHCII). CD74 does not seem to have an intracellular signaling domain and is, therefore, expected to initiate intracellular signaling by recruiting other membrane receptors such as CD44, CXCR2 and

CXCR4.^{3–5} These interactions are important for the role of MIF in inflammatory signaling. In addition, MIF has also been suggested as a target in cancer due to its downregulation of p53 and its overexpression in several cancer cell types.^{6–10} It was shown that neutralization of MIF through antibodies or genetic deletion was beneficial in several inflammatory disease models and a small molecule inhibitor of MIF was able to reduce tumor growth in mouse models.^{11–15} Taken together these data indicate that development of MIF binding molecules has potential for drug discovery for inflammatory diseases and cancer.

MIF is a small protein of 115 amino acids, weighing approximately 12.4 kDa and exists predominantly in a homotrimeric form. One human homologue has been described, D-dopachrome Tautomerase (D-DT or MIF2), which shows a similar function to MIF.¹⁶ MIF has structural similarity to two bacterial enzymes: 4-oxalocrotonate tautomerase (4-OT) and 5-carboxymethyl-2-hydroxymuconate isomerase.¹⁷ Inspired by these similarities, it was discovered that MIF not only functions as a cytokine, but has enzymatic activity as well. It has been shown to catalyze the interconversion of enol and keto isomers of D-Dopachrome and

* Corresponding author at: Antonius Deusinglaan 1, 9713AV Groningen, The Netherlands.

E-mail address: f.j.dekker@rug.nl (F.J. Dekker).

^f These authors contributed equally.

phenylpyruvate.¹⁸ One residue particularly important for this activity is the N-terminal proline which acts as a catalytic base in the tautomerase reaction.¹⁹ Screening for inhibitors of MIF tautomerase activity has been recognized as an efficient way to identify MIF binding compounds that can be further investigated in more advanced disease models where MIF has been shown to play a role. A well-known inhibitor of the MIF tautomerase activity is the isoxazoline (S,R)-3-(4-hydroxyphenyl)-4,5-dihydro-5-isoxazole acetic acid methyl ester (ISO-1, Fig. 1). ISO-1 is a competitive inhibitor of the MIF tautomerase activity and has beneficial effects in several disease models such as sepsis, chronic obstructive pulmonary disease (COPD) and cancer.^{15,20–23} Based on ISO-1, several other MIF inhibitors have been developed, among which are the biaryltriazoles.^{24–28} Using a structure-based virtual screening method, Orita-13 containing a chromen-4-one scaffold was identified as MIF inhibitor.^{26,29} Additionally, covalent MIF inhibitors have been described, such as TP, as probes suitable for activity-based protein profiling.³⁰ Taken together, several small molecule binders of MIF have been developed (Fig. 1), but the identification of novel structural classes remains needed for a better understanding of the structural requirements for binding and to provide a broader basis for drug discovery.

Here, we describe the identification of novel MIF binders inspired by the chromen-4-one scaffold of Orita-13. A focused compound collection of 57 compounds was synthesized using cyanoacetamide-based chemistry. Screening of this library for inhibition of MIF tautomerase activity provided 6 inhibitors with potencies in the low micromolar range. The structural motif that was identified expands the number of scaffold available for further development of MIF inhibitors towards applications in disease models.

2. Materials and methods

2.1. Chemistry general

All the reagents and solvents were purchased from Sigma-Aldrich, AK Scientific, Fluorochem, Abcr GmbH, or Acros and were used without further purification. All microwave irradiation reactions were carried out in a Biotage Initiator™ Microwave Synthesizer. Thin layer chromatography was performed on Millipore precoated silica gel plates (0.20 mm thick, particle size 25 μm). Nuclear magnetic resonance spectra were recorded on Bruker Avance 500 or 600 spectrometers (¹H NMR (500 MHz; 600 MHz), ¹³C NMR (126 MHz; 151 MHz). Chemical shifts for ¹H NMR were reported as δ values and coupling constants were in hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, ddd = doublet of doublet of doublets, m = multiplet. Chemical shifts for ¹³C NMR were reported in ppm relative to the solvent peak. Flash chromatography was performed on a Reveleris® X2 Flash Chromatography system, using Grace® Reveleris Silica flash cartridges (12 g). Mass

spectra were measured on a Waters Investigator Supercritical Fluid Chromatograph with a 3100 MS Detector (ESI) using a solvent system of methanol and CO₂ on a Viridis silica gel column (4.6 x 250 mm, 5 μm particle size) or Viridis 2-ethyl pyridine column (4.6 x 250 mm, 5 μm particle size). High resolution mass spectra were recorded using a LTQ-Orbitrap-XL (Thermo) at a resolution of 60,000@m/z400.

2.2. General procedure for the synthesis of 1–57

To a stirred solution of 2H-chromen-2-one (1.0 mmol) in dry ethanol (5 mL), the corresponding cyanoacetamide (1.0 mmol) and sodium ethoxide (0.2 mmol) were added. The reaction mixture was stirred at room temperature for 24 h. The precipitate was filtered off and washed with cold ethanol (2 x 5 mL), yielding the final compounds without further purification in yields ranging from 35 to 81%. The characterization of all compounds can be found in the [supporting information](#).

2.3. Single crystal x-ray structure determination

X-ray diffraction data for a single crystal of compound **7** was collected using a SuperNova (Rigaku-Oxford Diffraction) four circle diffractometer with a mirror monochromator and a microfocus MoKα radiation source (λ = 0.71073 Å). Additionally, the diffractometer was equipped with a CryoJet HT cryostat system (Oxford Instruments) allowing low temperature experiments, performed at 130 (2) K. The obtained data was processed with CrysAlisPro software (S1). The phase problem was solved by direct methods using SIR2004 (S2). Parameters of models were refined by full-matrix least-squares on F² using SHELXL-2014/6 (S3). Calculations were performed using WinGX integrated system (ver. 2014.1) (S4). Figure was prepared with Mercury 3.7 software (S5).

All non-hydrogen atoms were refined anisotropically. All hydrogen atoms attached to carbon atoms were positioned with the idealised geometry and refined using the riding model with the isotropic displacement parameter U_{iso}[H] = 1.2 (or 1.5 (methyl groups only)) U_{eq}[C]. Positions of hydrogen atoms linked to N2 were defined on the difference Fourier map and refined with no additional restraints. Crystal data and structure refinement results for presented crystal structure are shown in [Table S1](#). The molecular geometry (asymmetric unit) observed in the crystal structure is shown in [Fig. S1](#). Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 1575884.

2.4. MIF tautomerase activity assay

Tautomerase activity inhibition of MIF by the synthesized chromene compounds was measured using recombinantly expressed His-tagged MIF, which was purified with cOmplete His-Trap purification resin (Roche, The Netherlands). The assay was done following the procedure of Dziedzic et al.²⁶ 4-hydrox-

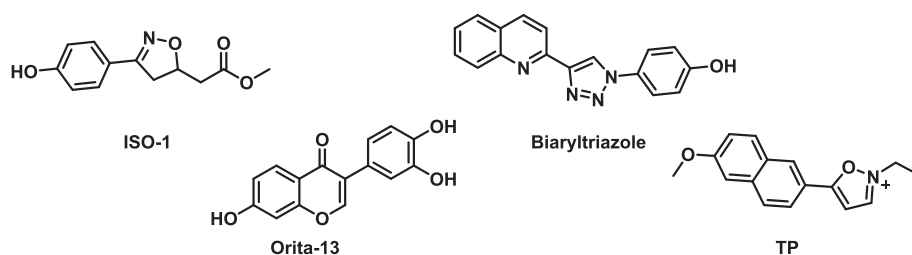


Fig. 1. Known MIF tautomerase activity inhibitors “ISO-1”, a “biaryltriazole”, “Orita-13” and activity-based probe “TP”.

4-phenyl pyruvate (4-HPP) was used as substrate to quantify tautomerase activity. Stock solutions of 10 mM 4-HPP were made in 50 mM ammonium acetate buffer pH 6.0, and incubated overnight at room temperature to allow equilibration between keto and enol form. Further dilutions of the substrate were made in the same acetate buffer. Inhibitor stock solutions had a concentration of 10 mM in DMSO. The inhibitor stock solutions were diluted in 0.4 M boric acid pH 6.2 to give final concentration in the screening assay of 25 and 50 μ M. For the IC₅₀ assay final concentrations of 250–0 μ M or 100–0 μ M or 25–0 μ M in 5% DMSO, with 2 or 1.6-fold dilution series were applied. The control contained 5% DMSO as a vehicle control. This amount did not influence the MIF tautomerase activity. In the assays 50 μ L of mixtures of MIF (dilution in 0.2 M boric acid pH 6.2, to give a final concentration of 340 nM) and the synthesized compounds were put in a UV-star F bottom 96-well plate. The enzymatic reaction was started by addition of 50 μ L 4-HPP (to give a final concentration of 0.5 mM), and the increase of absorbance at 306 nm was followed over time using a Spectrostar Omega BMG Labtech plate reader. The positive control contained all the components excluding inhibitor (but including 5% DMSO), and the negative control was as the positive control without MIF. The data obtained were analyzed by firstly taking the slopes of the linear part of the increased absorbance over the time (that is the velocity of the enzymatic reaction), then normalizing them to the positive and negative control to give percentage of inhibition.

2.5. Enzyme kinetic evaluation

To evaluate the reversibility of MIF tautomerase inhibition by the discovered chromene inhibitors, preincubation experiments were conducted using inhibitor **10** and **17**. The inhibitors (125–0 μ M, 1.6-fold dilution series in 5% DMSO) were preincubated with the enzyme (340 nM) for 2 min (the time of preincubation in the regular IC₅₀ assays) and 40 min prior to adding the substrate and starting the enzymatic reaction. Then the IC₅₀ curves were made as described above.

Dilution experiments were performed using inhibitor **10**. To do this, an initial mixture with a relatively high concentration of MIF (34 μ M) and the inhibitor (125 μ M in 5% DMSO) was made. Subsequently, this mixture was diluted 100 times in a solution containing the substrate 4-HPP (0.5 mM) and boric acid. A control assay was done following the same procedure without inhibitor, but containing 5% DMSO. The enzyme activity was measured as described before. The absorbance was plotted against time.

To further investigate the mechanism of inhibition, kinetic experiments were conducted using inhibitor **10**. The velocity of the enzymatic reaction was measured at increasing concentrations of 4-HPP (0–2.56 mM, 1.25 \times dilution) in the presence of MIF (340 nM) and inhibitor (0, 6.25 or 12.5 μ M). The velocity of the reaction was plotted against the concentration of 4-HPP using GraphPad Prism 5.0. The curve was plotted using enzyme kinetics-allosteric sigmoidal, yielding the $V_{\max \text{ app.}}$, Hill slope and $K_{\text{prime app.}}$. The concentration of 4-HPP that gives half of V_{\max} (K_{half}) was calculated from the K_{prime} using the following equation:

$$K_{\text{half}} = \frac{\text{Hillslope}}{\sqrt{K_{\text{prime}}}}$$

3. Results and discussion

3.1. Chemistry

A library of approximately 60 fused amino-2*H*-chromenopyridine-diones was synthesized using methods as initially described by Rosati et al. (Fig. 2A).^{31,32} The alignment of Orita-13 with the amino-2*H*-chromenopyridine-dione scaffold can be detected by checking the stereoscopic view of Orita-13, which indicates the potential of this library for MIF binding (Fig. 2B). These scaffolds combine a series of interesting features besides the chromene core, such as the amino group in 5-position and a fused piperidinodione ring. Moreover, the possibility to increase the diversity with two points of diversification and the rigid core structure attributed to the selection of this scaffold. It was possible to get the crystal structure of compound **7** revealing an intramolecular hydrogen bond between the exocyclic amine and the carbonyl group. This led to coplanarity between the fused rings, which provides interesting possibilities for the type of interactions under investigation (Fig. 2C, Fig. S1, Scheme S1).

Starting from our broad experience with cyanoacetamide chemistry in heterocycle synthesis,^{33–36} we elaborated on the synthesis of Rosati et al.,³¹ using a number of different cyanoacetamides and suitably substituted 2*H*-chromenes. Thus, we designed and synthesized a highly diverse medium-sized library in a medicinal chemistry frame utilizing aliphatic and aromatic substituents, heterocycles, hydrogen bond donors and acceptors. In addition, we enhanced the solubility of specific compounds with the introduction of morpholino substituents. The reactions proceeded under mild conditions with a plethora of different cyanoacetamides in good to very good yields in a parallel manner.

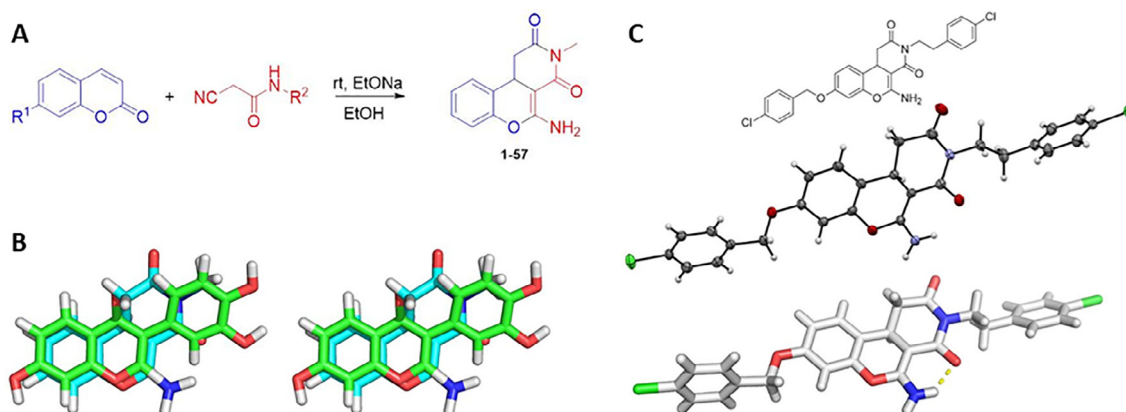
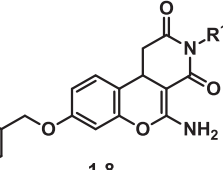
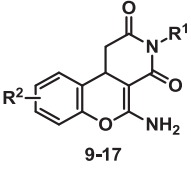




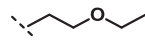


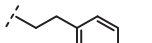
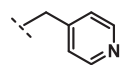
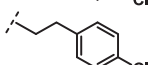
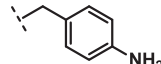
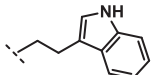
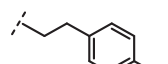
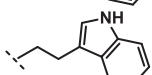
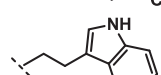
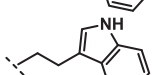
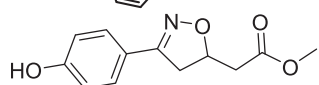
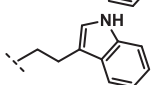


Fig. 2. A) Synthesis of fused amino-2*H*-chromenopyridine-diones. B) Stereoscopic view of the 3D-alignment of Orita-13 (green) with the amino-2*H*-chromenopyridine-dione scaffold (cyan). C) Structure of compound **7**, Molecular geometry observed in the crystal structures of compound **7**, showing the atom labelling scheme and an intramolecular hydrogen bond between the exocyclic amine and the carbonyl group is formed.

Table 1
Inhibition of MIF tautomerase activity by synthesized compounds of a chromene scaffold and reference compound ISO-1. IC₅₀ values were given as mean ± standard deviation of at least 2 independent experiments. ND = not determined.

								
Compound	R ¹	% inhibition at 25 μM	IC ₅₀ (μM)	Compound	R ¹	R ²	% inhibition at 25 μM	IC ₅₀ (μM)
1		40%	ND	9		3-OEt	60%	21 ± 2.1
2		10%	ND	10		H	60%	18 ± 3.5
3		10%	ND	11		4-Me	50%	ND
4		80%	7.1 ± 1.0	12		H	15%	ND
5		15%	ND	13		3-Me	5%	ND
6		45%	ND	14		3-OEt	10%	ND
7		80%	13 ± 1.1	15		H	15%	ND
8		70%	8.0 ± 1.0	16		4-Me	25%	ND
ISO-1			79 ± 3.7	17		3-Me	55%	6.2 ± 0.6

3.2. Biological evaluation

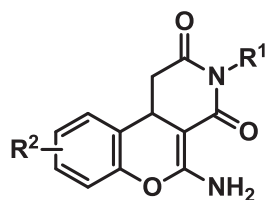
The compounds were tested for inhibition of the MIF tautomerase activity using a spectrophotometric assay based on the absorbance detection of the enzymatic enol product of 4-hydroxy phenylpyruvate (4-HPP) after reaction with boric acid.²⁶ First, a single point screening was done at a concentration of 25 μM and 50 μM and the compounds showing more than 50% inhibition of enzyme activity at 25 μM were tested for IC₅₀ values (Figs. S2 and S3).

The investigation started with 4-chlorobenzoyloxy chromene derivatives, bearing various aliphatic or aromatic substituents on the R¹ position (compounds 1–8, Table 2). Short aliphatic substituents (1–3) showed less than 50% inhibition at 25 μM, whereas compound 4 carrying a longer aliphatic substituent provided an IC₅₀ of 7.1 ± 1.0 μM. The compounds with aromatic substituent (5–8) also showed inhibition, of which a 4-chlorophenethyl substituent (7, IC₅₀ = 13 ± 1.1 μM) and an indole with ethyl spacer (8, IC₅₀ = 8.0 ± 1.0 μM) gave the best results. This suggests that lipophilic interactions are important for the inhibition of MIF. Next, these active derivatives (4, 7 and 8) were further investigated. To investigate whether the bulky 4-chlorobenzoyloxy was necessary, it was removed (R² = H) or replaced with several smaller substituents such as 3-Me, 4-Me or 3-OEt on the R² position (Table 1). In case of the long dodecane substituent (9–11), when smaller substituents on position R² were introduced, activity did not improve. In contrast, introducing smaller substitutions on R² in case of compounds with a 4-chlorophenethyl on position R¹ (12–13) caused a loss of activity. Concerning the indole substituted compounds (14–17), a methyl substituent at R² improved slightly the activity, but others were not active. Several other compounds were synthesized

combining different types of substituents at the R¹ position, such as morpholines, naphthalenes, furans, thiophenes or aliphatic chains with different heteroatoms (Table 2), but these did not lead to an improved inhibition. The IC₅₀ value of reference MIF inhibitor ISO-1 was determined under the conditions used for the chromene compounds. The IC₅₀ value of ISO-1 was within the range reported in literature.³⁷ The activity of Orita-13 has been reported to be similar to ISO-1.²⁷ The most potent chromene compounds were active at lower concentrations compared to the reference compound ISO-1. Therefore, compounds 10 and 17 were taken for further investigation.

3.3. Kinetic evaluation

To investigate the reversibility of the inhibition of MIF by the discovered inhibitors, a preincubation assay was performed with 10 and 17. The inhibitors were preincubated with MIF for 2 or 40 min before initiating the enzymatic reaction. Then, the IC₅₀ curve was made as described before. No difference in IC₅₀ was observed between incubation times, suggesting that the inhibition was not time-dependent on the investigated time scale (Fig. 3A, Fig. S4). To further investigate reversibility we performed dilution experiments with compound 10 in which the inhibitor and enzyme were preincubated at a high concentration (10 × IC₅₀) before dilution in a substrate solution to 10× below the IC₅₀ of the inhibitor. In combination with an irreversible inhibitor, the enzyme will show no activity after dilution. With a reversible inhibitor, however, the activity of the enzyme can be recovered.³⁸ The dilution assay with compound 10 showed that the activity of MIF could be recovered after dilution (Fig. 3B), which is consistent with reversible inhibition as observed in the preincubation assay.

Table 2Additional chromene compounds tested for inhibition of MIF. Percentage inhibition at 25 μ M is given as mean of at least 2 independent experiments.

Compound	R ¹	R ²	% inhibition at 25 μ M	Compound	R ¹	R ²	% inhibition at 25 μ M
8		3-OEt	30%	38		3-OMe	0%
19		4-Me	20%	39		H	0%
20		3-Me	20%	40		4-Me	15%
21		3-OEt	10%	41		3-OMe	15%
22		3-OMe	15%	42		4-Me	10%
23		4-Me	0%	43		3-OEt	0%
24		3-OMe	0%	44		3-OMe	0%
25		3-Me	0%	45		4-Me	0%
26		3-OEt	0%	46		3-Me	0%
27		3-OMe	0%	47		3-OEt	10%
28		4-Me	0%	48		3-OMe	0%
29		3-OMe	0%	49		4-Me	0%
30		H	0%	50		3-OEt	0%
31		4-Me	0%	51		3-OMe	0%
32		3-OEt	0%	52		H	0%
33		3-OMe	0%	53		4-Me	10%
34		3-Me	0%	54		3-Me	0%
35		3-OMe	0%	55		3-OEt	50%

(continued on next page)

Table 2 (continued)

Compound	R ¹	R ²	% inhibition at 25 μ M	Compound	R ¹	R ²	% inhibition at 25 μ M
36		3-Me	0%	56		3-OMe	25%
37		4-Me	0%	57		3-Me	35%

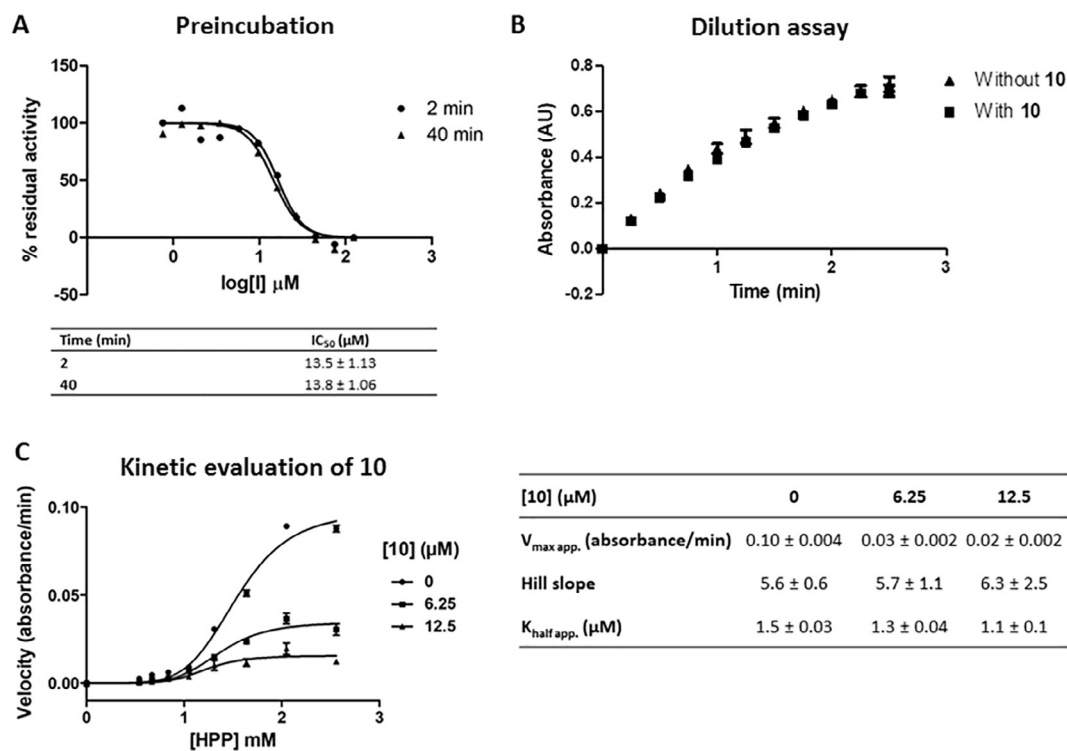


Fig. 3. A) MIF (340 nM) was preincubated with compounds **10** (125–0 μ M) for 2 or 40 min prior to starting the enzyme reaction by adding the substrate. No significant change in IC₅₀ value was observed. B) MIF (34 μ M) was incubated with a concentration of 125 μ M of compound **10**. Subsequently, this mixture was diluted 100x with the substrate and the enzyme activity was monitored. Diluting the inhibitor recovered the enzyme activity. C) The velocity of the enzyme reaction was measured at increasing concentrations of the substrate (4-HPP) in the presence of different concentrations of inhibitor **10**. The $V_{\max \text{ app.}}$, Hill slope and $K_{\text{half app.}}$ were determined for each inhibitor concentration.

To further investigate the mechanism of inhibition of the inhibitors, a kinetic evaluation of compound **10** was done (Fig. 3C). The velocity of the enzyme reaction was measured at increasing concentrations of the substrate (4-HPP) in the presence of different concentrations of inhibitor **10**. From this curve, the apparent maximum velocity ($V_{\max \text{ app.}}$), the Hill slope and the concentration of 4-HPP that gave half of $V_{\max \text{ app.}}$ ($K_{\text{half app.}}$) were determined. The experiment showed a sigmoidal curve with a Hill slope larger than 1, not following Michaelis-Menten kinetics, which is in line with observations from Lubetsky et al.³⁹ The K_{half} values were consistent with the values reported by Lubetsky et al. (denoted as $[S]_{0.5}$). An increasing concentration of compound **10** gave a decrease in $V_{\max \text{ app.}}$. The change in $K_{\text{half app.}}$ is less pronounced. This indicates that there is no direct competition between the substrate 4-HPP and the inhibitor **10**. This observation is in contrast to the binding mode described for Orita-13 that has been shown to bind the MIF active site.²⁹

4. Conclusions and future perspectives

MIF binding to its molecular targets plays a key role in inflammatory processes and cancer. Therefore, MIF binders are considered to be potential therapeutics. In this study, we employed the MIF tautomerase enzymatic activity to identify MIF binding compounds that could potentially interfere with MIF functions. Using cyanoacetamide chemistry a focused compound collection with a chromene scaffold was synthesized and subsequently screened for inhibition of MIF tautomerase activity. This enabled identification of several novel MIF inhibitors with IC₅₀'s in the low micromolar range. Kinetic evaluation suggested that compound **10** and **17** were reversible inhibitors and that inhibitor **10** does not bind in direct competition with the substrate 4-HPP. Taken together, a novel structural class of MIF inhibitors has been identified that could be used to further investigate the tautomerase activity of MIF and may ultimately lead to the development of novel therapeutic agents.

Acknowledgements

We thank Directorate General of Higher Education Indonesia (DIKTI) in collaboration with the University of Surabaya (Ubaya), Indonesia and the University of Groningen (RuG), The Netherlands, for giving a grant 94.18/E4.4/2014. We acknowledge the European Research Council for providing an ERC starting grant (309782) and the NWO for providing a VIDI grant (723.012.005) to F. J. Dekker. Research in Dömling research group was supported by the US National Institutes of Health (NIH) (2R01GM097082-05). Funding has been received from the European Union's Horizon 2020 research and innovation program under MSC ITN "Accelerated Early staGe drug dIScovery" (AEGIS, grant agreement No. 675555) and CoFund ALERT (grant agreement No. 665250). We thank the European Regional Development Fund in the framework of the Polish innovation Economy Operational Program (contract no. POIG.02.01.00-12-023/08) for financial support of J. Kalinowska-Tłuścik.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.bmc.2017.12.032>.

References

- Calandra T, Roger T. Macrophage migration inhibitory factor: a regulator of innate immunity. *Nat Rev Immunol*. 2003;3:791–800.
- Calandra T et al. The macrophage is an important and previously unrecognized source of macrophage migration inhibitory factor. *J Exp Med*. 1994;179:1895–1902.
- Shi X et al. CD44 is the signaling component of the macrophage migration inhibitory factor-CD74 receptor complex. *Immunity*. 2006;25:595–606.
- Leng L et al. MIF signal transduction initiated by binding to CD74. *J Exp Med*. 2003;197:1467–1476.
- Bernhagen J et al. MIF is a noncognate ligand of CXC chemokine receptors in inflammatory and atherogenic cell recruitment. *Nat Med*. 2007;13:587–596.
- Gordon-Weeks AN et al. Macrophage migration inhibitory factor: a key cytokine and therapeutic target in colon cancer. *Cytokine Growth Factor Rev*. 2015;26:451–461.
- Tomiyasu M et al. Quantification of macrophage migration inhibitory factor mRNA expression in non-small cell lung cancer tissues and its clinical significance. *Clin Cancer Res*. 2002;8:3755–3760.
- Xu X et al. Overexpression of macrophage migration inhibitory factor induces angiogenesis in human breast cancer. *Cancer Lett*. 2008;261:147–157.
- Munaut C et al. Macrophage migration inhibitory factor (MIF) expression in human glioblastomas correlates with vascular endothelial growth factor (VEGF) expression. *Neuropathol Appl Neurobiol*. 2002;28:452–460.
- Shimizu T et al. High expression of macrophage migration inhibitory factor in human melanoma cells and its role in tumor cell growth and angiogenesis. *Biochem Biophys Res Commun*. 1999;264:751–758.
- Bernhagen J et al. MIF is a pituitary-derived cytokine that potentiates lethal endotoxaemia. *Nature*. 1993;365:756–759.
- Bozza M et al. Targeted disruption of migration inhibitory factor gene reveals its critical role in sepsis. *J Exp Med*. 1999;189:341–346.
- de Jong YP et al. Development of chronic colitis is dependent on the cytokine MIF. *Nat Immunol*. 2001;2:1061–1066.
- Mikulowska A et al. Macrophage migration inhibitory factor is involved in the pathogenesis of collagen type II-induced arthritis in mice. *J Immunol*. 1997;158(11):5514–5517.
- Ioannou K et al. ISO-66, a novel inhibitor of macrophage migration, shows efficacy in melanoma and colon cancer models. *Int J Oncol*. 2014;45:1457–1468.
- Merk M et al. D-dopachrome tautomerase (D-DT or MIF-2): doubling the MIF cytokine family. *Cytokine*. 2012;59:10–17.
- Suzuki M et al. Crystal structure of the macrophage migration inhibitory factor from rat liver. *Nat Struct Biol*. 1996;3:259–266.
- Rosengren E et al. The macrophage migration inhibitory factor MIF is a phenylpyruvate tautomerase. *FEBS Lett*. 1997;417:85–88.
- Lubetsky JB et al. Pro-1 of macrophage migration inhibitory factor functions as a catalytic base in the phenylpyruvate tautomerase activity. *Biochemistry*. 1999;38:7346–7354.
- Lubetsky JB et al. The tautomerase active site of macrophage migration inhibitory factor is a potential target for discovery of novel anti-inflammatory agents. *J Biol Chem*. 2002;277:24976–24982.
- Al-Abed Y et al. ISO-1 binding to the tautomerase active site of MIF inhibits its pro-inflammatory activity and increases survival in severe sepsis. *J Biol Chem*. 2005;280:36541–36544.
- Russell KE et al. The MIF Antagonist ISO-1 Attenuates Corticosteroid-Insensitive Inflammation and Airways Hyperresponsiveness in an Ozone-Induced Model of COPD. *PLoS One*. 2016;11:e0146102.
- Al-Abed Y, VanPatten S. MIF as a disease target: ISO-1 as a proof-of-concept therapeutic. *Future Med Chem*. 2011;3:45–63.
- Balachandran S et al. Synthesis and biological activity of novel MIF antagonists. *Bioorg Med Chem Lett*. 2011;21:1508–1511.
- Alam A et al. Synthesis and bio-evaluation of human macrophage migration inhibitory factor inhibitor to develop anti-inflammatory agent. *Bioorg Med Chem*. 2011;19:7365–7373.
- Dziedzic P et al. Design, synthesis, and protein crystallography of biaryltriazoles as potent tautomerase inhibitors of macrophage migration inhibitory factor. *J Am Chem Soc*. 2015;137:2996–3003.
- Cisneros JA et al. A fluorescence polarization assay for binding to macrophage migration inhibitory factor and crystal structures for complexes of two potent inhibitors. *J Am Chem Soc*. 2016;138:8630–8638.
- Jorgensen WL et al. Receptor agonists of macrophage migration inhibitory factor. *Bioorg Med Chem Lett*. 2010;20:7033–7036.
- Orita M et al. Coumarin and chromen-4-one analogues as tautomerase inhibitors of macrophage migration inhibitory factor: discovery and X-ray crystallography. *J Med Chem*. 2001;44:540–547.
- Qian Y et al. Activity-based proteome profiling probes based on Woodward's Reagent K with distinct target selectivity. *Angew Chem Int Ed Engl*. 2016;55:7766–7771.
- Rosati O et al. Synthesis of 5-amino-1,10b-dihydro-2H-chromeno[3,4-c]pyridine-2,4(3H)-diones from coumarins and cyanoacetamides under basic conditions. *Synthesis-stuttgart*. 2010;2:239–248.
- Curini M et al. Preparation of 2-amino-4H-chromene derivatives from coumarins in basic media. *Eur J Org Chem*. 2006;3:746–751.
- Wang K, Herdtweck E, Dömling A. Cyanoacetamides (IV): versatile one-pot route to 2-quinoline-3-carboxamides. *ACS Comb Sci*. 2012;14:316–322.
- Wang K et al. Cyanoacetamide multicomponent reaction (I): parallel synthesis of cyanoacetamides. *J Comb Chem*. 2009;11:920–927.
- Wang K, Kim D, Dömling A. Cyanoacetamide MCR (III): three-component Gewald reactions revisited. *J Comb Chem*. 2010;12:111–118.
- Wang K, Herdtweck E, Dömling A. One-pot synthesis of 2-amino-indole-3-carboxamide and analogous. *ACS Comb Sci*. 2011;13:140–146.
- Cisneros JA et al. Irregularities in enzyme assays: the case of macrophage migration inhibitory factor. *Bioorg Med Chem Lett*. 2016;26:2764–2767.
- Strelow J et al. Mechanism of action assays for enzymes. In: Sittampalam GS et al., eds. *Assay guidance manual*. MD: Bethesda; 2004.
- Lubetsky JB et al. Pro-1 of macrophage migration inhibitory factor functions as a catalytic base in the phenylpyruvate tautomerase activity. *Biochemistry*. 1999;38:7346–7354.

BIOORGANIC & MEDICINAL CHEMISTRY

Editor-in-Chief: Professor H. Waldmann, Department of Chemical Biology,
Max-Planck-Institut für Molekulare Physiologie, Otto-Hahn-Strasse 11, 44227 Dortmund, Germany
Fascimile: (49) 231 133 2499

Editor: Professor Y. Hashimoto, Institute of Molecular & Cellular Biosciences,
The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan
Fascimile: (81) 3 5841 8495

Editor: Professor K. D. Janda, The Scripps Research Institute, Department of Chemistry,
The Skaggs Institute for Chemical Biology, The Worm Institute of Research & Medicine, 10550 North Torrey Pines Road,
La Jolla, CA 92037, USA
Fascimile: (1) 858 784 2595

Editor: Professor X. Lei, Department of Chemical Biology, College of Chemistry and Molecular Engineering,
Peking University (PKU), Beijing 100871, China
Phone: (86) 10 62760292

EXECUTIVE BOARD OF EDITORS FOR TETRAHEDRON PUBLICATIONS

Chairman: **Professor S. F. Martin**

Dr. P. R. Bernstein, Department of Chemistry and Biochemistry,
102 Brown Laboratory, University of Delaware, Newark, DE 19716, USA

Professor M. Christmann, Institute of Chemistry and Biochemistry,
Freie Universität Berlin, Berlin, Germany

Professor S. G. Davies, Dyson Perrins Laboratory,
Department of Chemistry, University of Oxford, Oxford OX1 3QY, UK

Professor M. D. Disney, Department of Chemistry, The Scripps Research
Institute, Jupiter, FL 33458, USA

Professor L. Ghosez, l'Institut Européen de Chimie et de Biologie (IECB),
33607 Pessac Cedex, France

Professor Y. Hashimoto, Institute of Molecular & Cellular Biosciences,
The University of Tokyo, III-Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan

Professor T. Hayashi, Institute of Materials Research and Engineering (IMRE),
Singapore

Professor J. Hu, Chinese Academy of Sciences (CAS), Shanghai, China

Professor K. D. Janda, Department of Chemistry,
The Scripps Research Institute, La Jolla, CA 92037, USA

Professor M. Kitamura, Graduate School of Pharmaceutical Sciences, Dept. of
Basic Medicinal Sciences, Nagoya University, Chikusa 464-8602, Nagoya, Japan

Professor G.-Q. Lin, Shanghai Institute of Organic Chemistry,
Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

Professor S. F. Martin, Department of Chemistry & Biochemistry,
University of Texas, Austin, TX 78712, USA

Professor K. Maruoka, Department of Chemistry, Kyoto University,
Kyoto 606-8502, Japan

Professor S. Neidle, UCL School of Pharmacy, University College London,
London WC1N 1AX, UK

Professor G. P. Pandey, Sanjay Gandhi Post Graduate Institute of Medical
Sciences (SGPGI), Lucknow, India

Professor M. Shibasaki, Graduate School of Pharmaceutical Sciences,
The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Professor V. K. Singh, IISER Bhopal, Bhopal, India

Professor B. M. Stoltz, California Institute of Technology, Pasadena, California,
USA

Professor R. J. K. Taylor, Department of Chemistry, University of York,
Heslington, York YO10 5DD, UK
(Associate Editors, Dr P. A. O'Brien and Dr D. K. Smith)

Professor K. Tomioka, Graduate School of Pharmaceutical Sciences,
Department of Synthetic Medicinal Chemistry, Kyoto University,
Kyoto 606-8501, Japan

Professor H. Waldmann, Max-Planck-Inst. für Molekular Physiologie,
Department of Chemistry, Otto-Hahn-Strasse 11, 44227 Dortmund, Germany

Professor J. Wood, Department of Chemistry & Biochemistry,
Baylor University, Waco, Texas 76798, USA

Professor J. Zhu, École Polytechnique Fédérale de Lausanne (EPFL),
Lausanne-Dorigny, Switzerland

ADVISORY BOARD

C. R. Bertozzi, Berkeley, CA

B. S. J. Blagg, Lawrence, KS

M.-J. Blanco, Cambridge, MA

M. Chu-Moyer, Cambridge, MA

P. Gmeiner, Erlangen

D. Hilvert, Zürich

L. C. Hsieh-Wilson, Pasadena, CA

M. Ishibashi, Chiba

W. L. Jorgensen, New Haven, CT

B. M. Kim, Seoul

M. Köhn, Heidelberg

K. Lackey, Charleston, SC

J. Lee, Seoul

C. E. Müller, Bonn

H. S. Overkleeft, Leiden

P. G. Schultz, La Jolla, CA

P. Seeburger, Zürich

O. Seitz, Berlin

K. Shokat, San Francisco, CA

R. Silverman, Evanston, IL

C. T. Supuran, Firenze

H. Takahashi, Tokyo

S. Walker, Cambridge, MA

S. Ward, Brighton, UK

P. A. Wender, Stanford, CA

N. Winssinger, Geneva

C.-H. Wong, La Jolla, CA

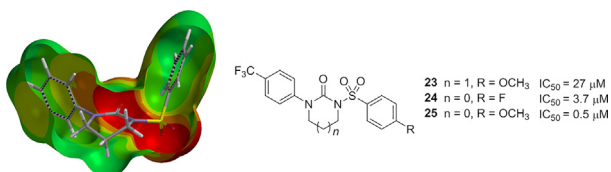
W.-L. Zhu, Shanghai

Articles

Design, synthesis, and biological evaluation of inhibitors of the NADPH oxidase, Nox4

pp 989–998

Qian Xu, Amol A. Kulkarni*, Ayyiliath M. Sajith, Dilbi Hussein, David Brown, Osman F. Güner, M. Damoder Reddy, E. Blake Watkins, Bernard Lassègue, Kathy K. Griendling, J. Phillip Bowen*

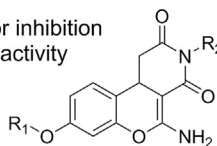


Discovery of chromenes as inhibitors of macrophage migration inhibitory factor

pp 999–1005

Tjie Kok, Hannah Wapenaar, Kan Wang, Constantinos G. Neochoritis, Tryfon Zarganes-Tzitzikas, Giordano Proietti, Nikolaos Eleftheriadis, Katarzyna Kurpiewska, Justyna Kalinowska-Tłuścik, Robbert H. Cool, Gerrit J. Poelarends, Alexander Dömling, Frank J. Dekker*

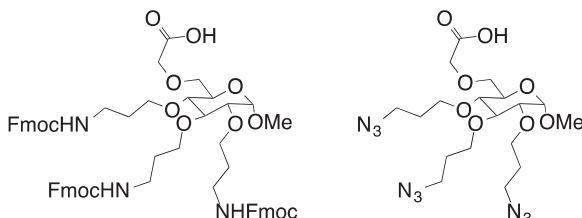
Novel structural class for inhibition
of MIF tautomerase activity



New branched amino acids for high affinity dendrimeric DC-SIGN ligands

pp 1006–1015

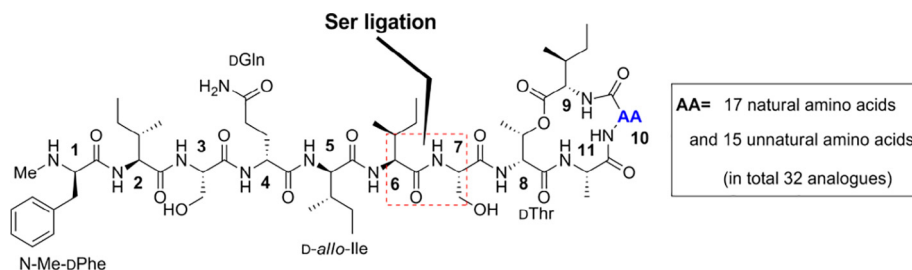
Laurent Cattiaux, Vanessa Porkolab, Franck Fieschi, Jean-Maurice Mallet*



Synthesis and antibacterial studies of teixobactin analogues with non-isostere substitution of enduracididine

pp 1062–1068

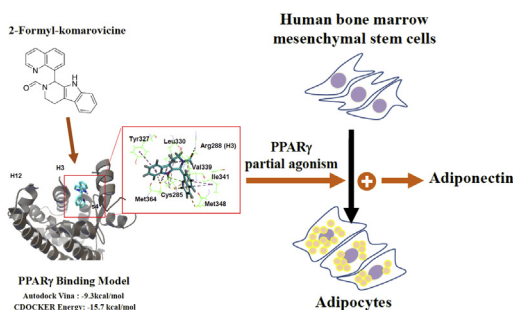
Kang Jin, Kathy Hiu Laam Po, Wang Yeuk Kong, Chung Hei Lo, Chun Wah Lo, Ho Yin Lam, Amaya Sirinimal, Jonathan Avraham Reuven, Sheng Chen*, Xuechen Li*



2-Formyl-komarovicine promotes adiponectin production in human mesenchymal stem cells through PPAR γ partial agonism

pp 1069–1075

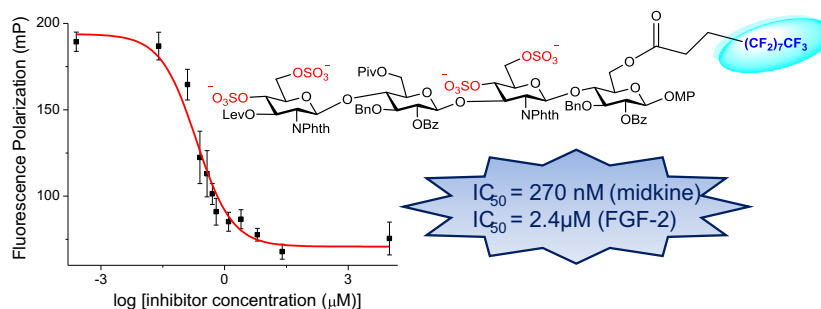
Sungjin Ahn, Moonyoung Lee, Seungchan An, Sooyeol Hyun, Jiho Hwang, Jongkook Lee*, Minsoo Noh*



Fluorous-tag assisted synthesis of a glycosaminoglycan mimetic tetrasaccharide as a high-affinity FGF-2 and midkine ligand

pp 1076–1085

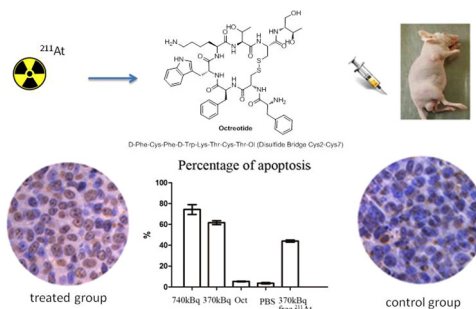
Susana Maza, Noel Gandia-Aguado, José L. de Paz*, Pedro M. Nieto*



Evaluation of astatine-211-labeled octreotide as a potential radiotherapeutic agent for NSCLC treatment

pp 1086–1091

Bingkun Zhao, Shanshan Qin, Li Chai, Gaixia Lu, Yuanyou Yang, Huawei Cai, Xueyu Yuan, Suyun Fan*, Qingqing Huang*, Fei Yu*



Bioorganic and Medicinal Chemistry

COUNTRY	SUBJECT AREA AND CATEGORY	PUBLISHER	H-INDEX
United Kingdom	Biochemistry, Genetics and Molecular Biology	Elsevier Ltd.	179
	Chemistry		
	Pharmacology, Toxicology and Pharmaceutics		

PUBLICATION TYPE	ISSN	COVERAGE	INFORMATION
Journals	14643391, 09680896	1993-2022	Homepage How to publish in this journal Contact

SCOPE

Bioorganic & Medicinal Chemistry publishes complete accounts of research of outstanding significance and timeliness on all aspects of molecular interactions at the interface of chemistry and biology, together with critical review articles. The journal publishes reports of experimental results in medicinal chemistry, chemical biology and drug discovery and design, emphasizing new and emerging advances and concepts in these fields. The aim of the journal is to promote a better understanding at the molecular level of life processes, and living organisms, as well as the interaction of these with chemical agents. The Journal welcomes papers on: the medicinal chemistry and associated biology (including target identification and validation) of established or new disease targets- the reporting of the discovery, design or optimization of potent new compounds or biological agents- the analysis and discussion of structure-activity relationships and pharmacological issues relevant to drug design and action using in vitro and in vivo models, including the use of computational techniques when closely linked to experimental data- the

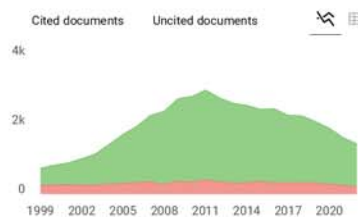
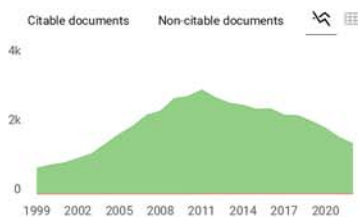
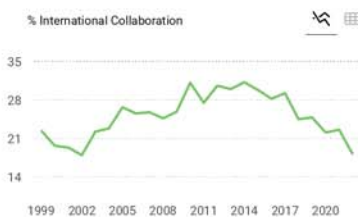
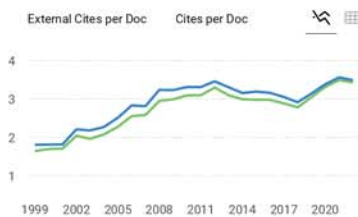
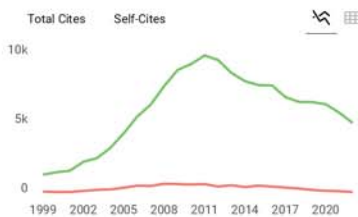
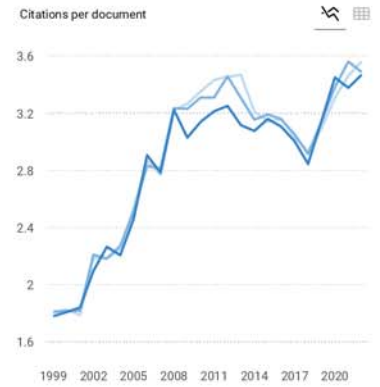
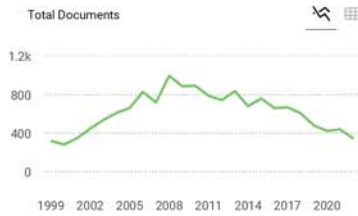
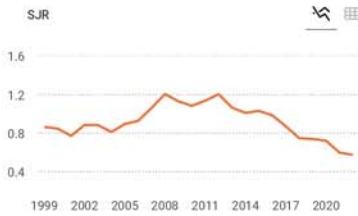
1

2

3

4

5



Bioorganic and Medicinal Chemistry

Q2 Clinical Biochemistry best quartile

SJR 2022 0.57

powered by scimagojr.com

Show this widget in your own website

Just copy the code below and paste within your html code:

```
<a href="https://www.scimagojr.com">
```

SCImago Graphica

Explore, visually communicate and make sense of data with our new data visualization tool.



Metrics based on Scopus® data as of April 2023

Leave a comment

Name

Email

(will not be published)

Submit

The users of Scimago Journal & Country Rank have the possibility to dialogue through comments linked to a specific journal. The purpose is to have a forum in which general doubts about the processes of publication in the journal, experiences and other issues derived from the publication of papers are resolved. For topics on particular articles, maintain the dialogue through the usual channels with your editor.

Developed by:



Powered by:



Follow us on @ScimagoJR

Scimago Lab, Copyright 2007-2022. Data Source: Scopus®

EST MODUS IN REBUS
Horacio (Salvo 1.1.106)

[Cookie settings](#)

[Cookie policy](#)



Source details

Bioorganic and Medicinal Chemistry

Scopus coverage years: from 1993 to Present

Publisher: Elsevier

ISSN: 0968-0896 E-ISSN: 1464-3391

Subject area: [Chemistry: Organic Chemistry](#) [Pharmacology, Toxicology and Pharmaceutics: Pharmaceutical Science](#)
[Pharmacology, Toxicology and Pharmaceutics: Drug Discovery](#) [View all](#) ∨

Source type: Journal

CiteScore 2022 **6.4** ⓘ

SJR 2022 **0.573** ⓘ

SNIP 2022 **0.860** ⓘ

[View all documents](#) >

[Set document alert](#)

[Save to source list](#) [Source Homepage](#)

[CiteScore](#) [CiteScore rank & trend](#) [Scopus content coverage](#)

CiteScore 2022 ∨

$$6.4 = \frac{10,762 \text{ Citations 2019 - 2022}}{1,671 \text{ Documents 2019 - 2022}}$$

Calculated on 05 May, 2023

CiteScoreTracker 2023 ⓘ

$$5.6 = \frac{7,387 \text{ Citations to date}}{1,327 \text{ Documents to date}}$$

Last updated on 05 July, 2023 • Updated monthly

CiteScore rank 2022 ⓘ

Category	Rank	Percentile
Chemistry		
Organic Chemistry	#50/197	74th
Pharmacology, Toxicology and Pharmaceutics		
Pharmaceutical Science	#50/171	71st

[View CiteScore methodology](#) > [CiteScore FAQ](#) > [Add CiteScore to your site](#)

About Scopus

[What is Scopus](#)

[Content coverage](#)

[Scopus blog](#)

[Scopus API](#)

[Privacy matters](#)

Language

[日本語版を表示する](#)

[查看简体中文版本](#)

[查看繁體中文版本](#)

[Просмотр версии на русском языке](#)

Customer Service

[Help](#)

[Tutorials](#)

[Contact us](#)

ELSEVIER

[Terms and conditions](#) ↗ [Privacy policy](#) ↗

Copyright © Elsevier B.V. ↗ . All rights reserved. Scopus® is a registered trademark of Elsevier B.V.

We use cookies to help provide and enhance our service and tailor content. By continuing, you agree to the use of cookies ↗.

