Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2024, **22**, 6532

Iodine/Oxone® oxidative system for the synthesis of selenylindoles bearing a benzenesulfonamide moiety as carbonic anhydrase I, II, IX, and XII inhibitors†

Martina Palomba,‡[a] Andrea Angeli,‡[b] Riccardo Galdini,[a] Alexandra Joana Hughineata,[a] Gelson Perin,[c] Eder João Lenardão,[c] Francesca Marini,[a] Claudio Santi,*[a] Claudiu T. Supuran[b] and Luana Bagnoli*[a]

Received 19th May 2024,
Accepted 19th July 2024

DOI: 10.1039/d4ob00826j

rsc.li/obc

A wide range of 3-selenylindoles were synthesized *via* an eco-friendly approach that uses Oxone® as the oxidant in the presence of a catalytic amount of iodine. This mild and economical protocol showed broad functional group tolerance and operational simplicity. A series of novel selenylindoles bearing a benzenesulfonamide moiety were also synthesized and evaluated as carbonic anhydrase inhibitors of the human (h) isoforms hCa I, II, IX, and XII, which are involved in pathologies such as glaucoma and cancer. Several derivatives showed excellent inhibitory activity towards these isoforms in the nanomolar range, lower than that shown by acetazolamide.

Introduction

N-Heterocycles play pivotal roles in chemistry and biology because they are ubiquitous in nature and are privileged scaffolds in medicinal chemistry.[1] For example, indoles are considered highly significant molecules in the medical field due to their prevalence in drugs approved for the treatment of various diseases.[2] In the past years, great attention has been paid to the incorporation of selenium moieties into bioactive heterocycles and natural products.[3] Xu also tried to correlate the chemical properties of selenium with the pharmacological activities of selenobioactive compounds.[3c] These derivatives have emerged as potential therapeutic agents for the treatment of a range of diseases, acting as antitumoral, antiviral, and antimicrobial agents in addition to presenting a series of antioxidant properties.[4] In this field, 3-selenylindoles are currently receiving increasing attention because of their pharmacological properties. As highlighted in Fig. 1, 3-selenylindoles and their corresponding selenoxides show antiproliferative properties and are active *in vitro* against cancer cells, acting as combretastatin A-4 analogs.[5] Other derivatives presented antidepressant-like activity in mice[6] and anti-inflammatory properties with potential application in the treatment of diseases associated with oxidative damage.[7,4d] Due to the important applications of 3-chalcogenylindoles, the development of methods for the synthesis of selenylindoles has increased in the past few years.

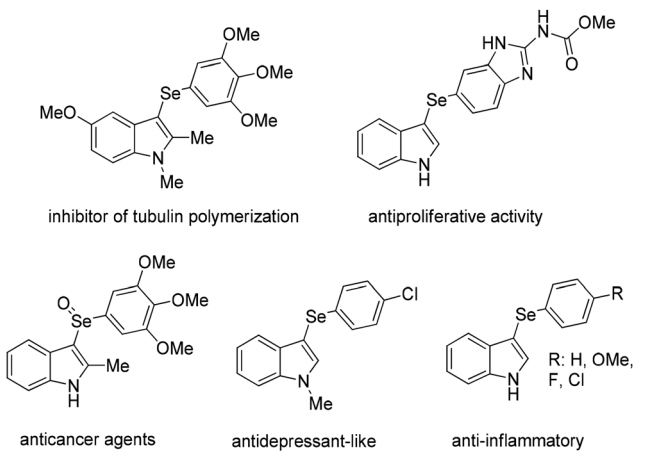


Fig. 1 Biologically relevant 3-selenylindoles.

[a]*Department of Pharmaceutical Sciences (Group of Catalysis, Synthesis and Organic Green Chemistry), University of Perugia, Via del Liceo, 1-06123 Perugia, Italy. E-mail: luana.bagnoli@unipg.it, claudio.santi@unipg.it*

[b]*University of Florence, NEUROFARBA Dept., Sezione di Scienze Farmaceutiche, Via Ugo Schiff 6, 50019 Sesto Fiorentino, Italy*

[c]*Laboratório de Síntese Orgânica Limpa (LASOL), Centro de Ciências Químicas, Farmacêuticas e de Alimentos (CCQFA), Universidade Federal de Pelotas (UFPel), P. O. Box 354, CEP: 96010-900 Pelotas, RS, Brazil*

†Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d4ob00826j

‡These authors contributed equally to this work.

In the case of the formation of C–Se bonds, one traditional method involves direct C(sp^2)–H functionalization of indoles with diorganoyl diselenides catalysed by metals.[8] Several approaches based on the use of transition metal-free conditions are also available in the literature. Commonly, they involve direct selenylations of the indole nucleus with various electrophilic reagents generated in the presence of oxidants.[9] Base-promoted[10] and photo[11] or electrochemical[12] reactions have also been investigated (Fig. 2). In continuation of our interest in the development of new C(sp^2)–H functionalized eco-friendly processes and considering our long-standing interest in the indole nucleus,[13] in this paper, we describe an alternative and general procedure for the regioselective synthesis of 3-selenylindoles. This sustainable approach uses Oxone® as the oxidant in the presence of a catalytic amount of iodine. Novel 3-selenylindoles bearing a benzenesulfonamide moiety could be prepared as potential inhibitors of human carbonic anhydrase (hCA). CAs are metalloenzymes that catalyse a very simple reaction, the hydration of carbon dioxide to bicarbonate and protons.[14] These enzymes are involved in a variety of diseases such as glaucoma, retinitis pigmentosa, epilepsy, and arthritis, and in the development of tumours. Recently, some of us reported that selenols, selenoureas, diselenides, and selenides containing a benzenesulfonamide moiety show relevant hCA-inhibitory activity.[15]

Results and discussion

Initially, we started our exploration focusing on the reaction between the 1*H*-indole **1a** and the diphenyl diselenide **2a**, aiming to prepare the 3-(phenylselanyl)-1*H*-indole **3a**.

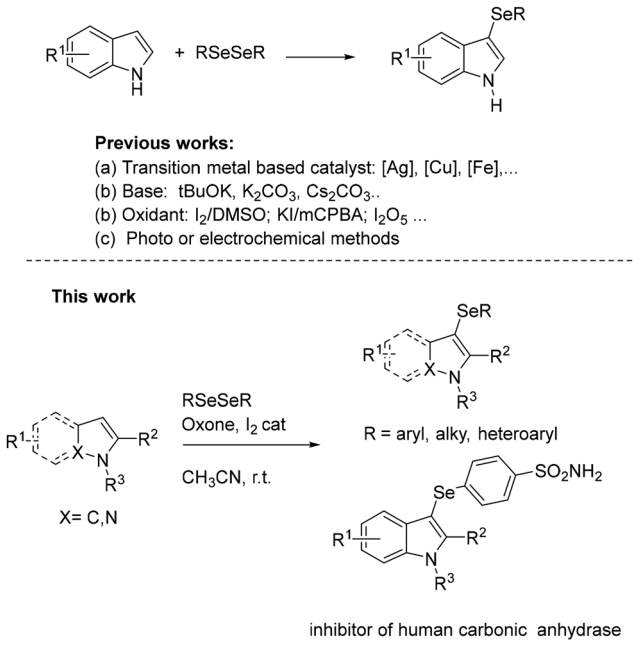
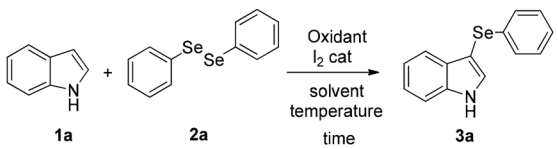


Fig. 2 Different strategies for the synthesis of 3-selenylindoles.

Preliminary investigations to produce electrophilic selenium species were carried out using various oxidants, such as phenyliodine diacetate (PID, Table 1, entries 1–4), ammonium persulfate (entry 5), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, entry 6), in stoichiometric or over-stoichiometric amounts, and the expected 3-selenylindole **3a** was obtained only in low yields. Recently, some authors have explored the use of Oxone® as the oxidant in selenocyclization reactions to prepare seleno-functionalized heterocycles.[16] Oxone® ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) is a stable, easy to handle, eco-friendly and cheap triple salt.[17] Unfortunately, when Oxone® was used in acetonitrile, the reaction did not proceed well (entry 7). However, in the presence of iodine (20 mol%) under an air atmosphere, the selenenylated product **3a** was isolated in good yield (entry 8), comparable to that obtained with stoichiometric iodine[9f] (entry 9), but in a shorter reaction time. In recent years, iodine has emerged as a catalyst of choice in numerous selenylation reactions, including those involving alkenes, aromatic, and (hetero)cyclic compounds.[18] The influence of temperature, solvents or loading of catalyst was then investigated. As shown in Table 1, increasing the temperature from room temperature to 50 °C resulted in a decrease in the yield (entry 10). Furthermore, decreasing the catalyst loading to 10 mol% and 5 mol% reduced the yield to 66% (entry 11) and 42% (entry 12), respectively. Some polar and apolar solvents (entries 13–17) were then screened. Good yields of product **3a** were obtained using polar solvents with

Table 1 Optimization of the reaction conditions



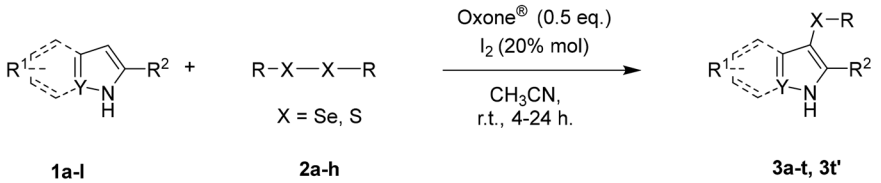
Entry[a]	Oxidant (eq.)	I_2 (% mol)	T (°C)	Time (h)	Solvent	Yield (%)
1	PID (0.8)	—	r.t.	24	MeOH	13
2	PID (2)	—	r.t.	36	MeOH	7
3[b]	PID (2)	—	r.t	24	CH_3CN	10
4	PID (0.8)	—	80	28	CH_3CN	15
5	$(NH_4)_2S_2O_8$ (0.6)	—	80	24	CH_3CN	25
6	DDQ (2)	—	80	24	MeOH	18
7	Oxone (0.5)	—	r.t.	18	CH_3CN	20
8	**Oxone (0.5)**	**20**[c]	**r.t.**	**4**	**CH_3CN**	**70**
9		50[c]	r.t.	28	CH_3CN	67
10	Oxone (0.5)	20[c]	50	5	CH_3CN	50
11	Oxone (0.5)	10[c]	r.t.	4	CH_3CN	66
12	Oxone (0.5)	5[c]	r.t.	24	CH_3CN	42
13	Oxone (0.5)	20[c]	r.t.	5	MeOH	60
14	Oxone (0.5)	20[c]	r.t.	7	DMF	55
15	Oxone (0.5)	20[c]	r.t.	8	THF	63
16	Oxone (0.5)	20[c]	r.t.	27	CH_2Cl_2	45
17	Oxone (0.5)	20[c]	r.t.	20	Toluene	43
18[d]	Oxone (0.5)	20[c]	r.t.	4	CH_3CN	44

[a] Reaction conditions: indole **1a** (1 eq.), diphenyl diselenide **2a** (0.5 eq.), Oxone® (0.5 eq.), solvent (5.0 mL), in air. [b] Indole **1a** was used in excess (5 eq.). [c] Iodine amount (50, 20, 10, and 5 mol%) with respect to indole **1a**. [d] Reaction was carried out in an argon atmosphere.

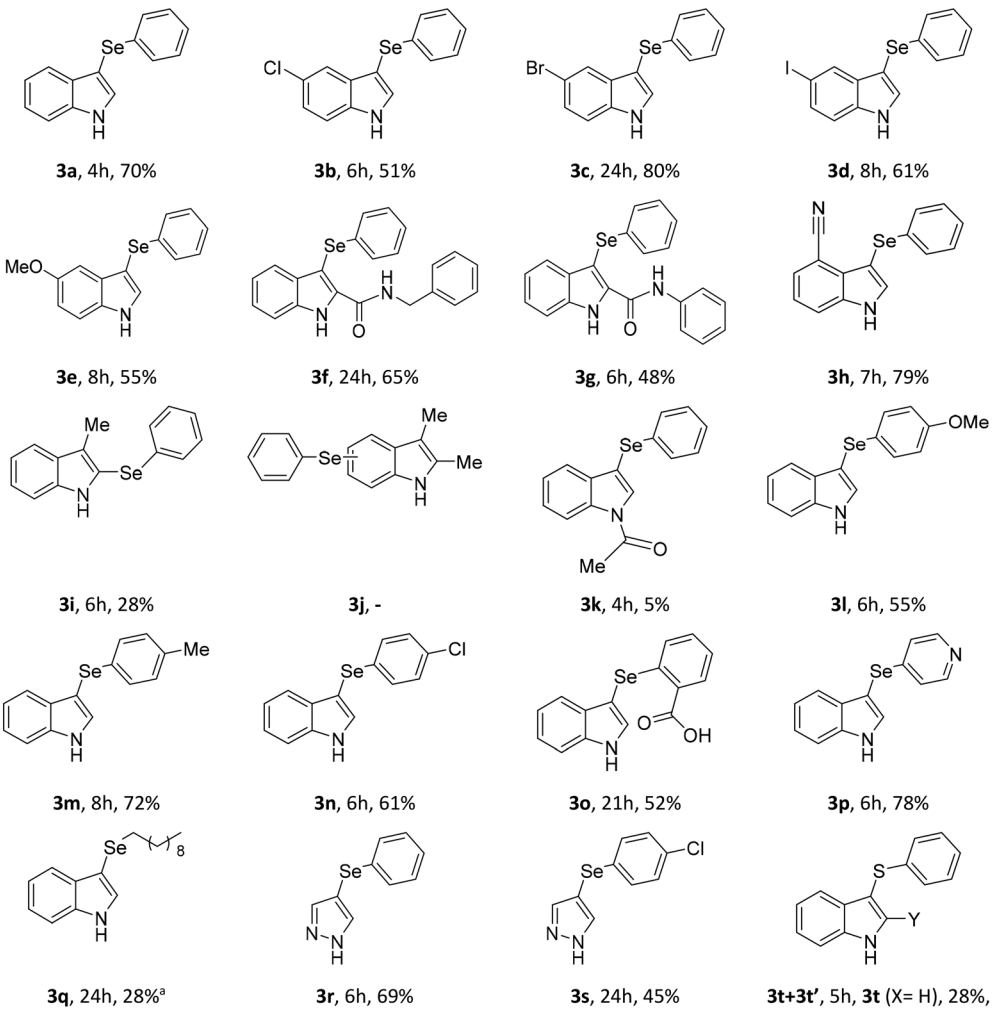
respect to nonpolar ones, but acetonitrile remains the most efficient for this process. Moreover, when the reaction was performed under an argon atmosphere, a decrease in the yield was observed (44% yield, entry 18), demonstrating the beneficial effect of the air atmosphere.

With the optimized conditions in hand (Table 1, entry 8), a small library of 3-selenylindoles was created to evaluate the scope and the limitation of the protocol. The scope of the reaction was examined with indoles containing various functional groups and with differently substituted diselenides (Table 2). Several 5-substituted indoles, including chloro, bromo, iodo and methoxy, are suitable substrates, affording the corresponding products **3b–e** in 51–80% yields. The effect of the substitution at the 2- and 4-positions of the indole was also evaluated. The electronic and steric effects of the amide groups at the 2-position of the indole were tolerated, and novel 2-carboxamide-3-selenylindoles **3f** and **3g** were obtained in satisfactory yields. When a cyano group was present at the C4 position, the corresponding 3-selenylindole **3h** was obtained in a high yield. If the C3-position of indole ring is occupied by a methyl group, only 28% of the 2-selenylindole **3i** was formed, while the reaction failed in the case of compound **3j**, in which both 2- and 3-positions are substituted. The *N*-acetyl indole was also tested but only a 5% yield of product **3k** was obtained. Next, several

Table 2 Substrate scope: substituted indoles and pyrazoles with different diorganyl dichalcogenides



1a-l **2a-h** **3a-t, 3t'**



3a, 4h, 70% **3b**, 6h, 51% **3c**, 24h, 80% **3d**, 8h, 61%

3e, 8h, 55% **3f**, 24h, 65% **3g**, 6h, 48% **3h**, 7h, 79%

3i, 6h, 28% **3j**, - **3k**, 4h, 5% **3l**, 6h, 55%

3m, 8h, 72% **3n**, 6h, 61% **3o**, 21h, 52% **3p**, 6h, 78%

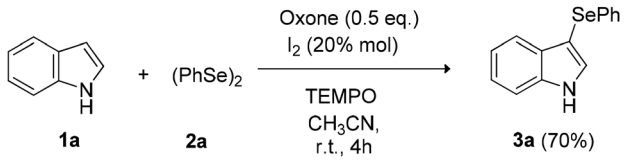
3q, 24h, 28%[a] **3r**, 6h, 69% **3s**, 24h, 45% **3t+3t'**, 5h, **3t** (X= H), 28%,

[a] Using 5 mol% of iodine.

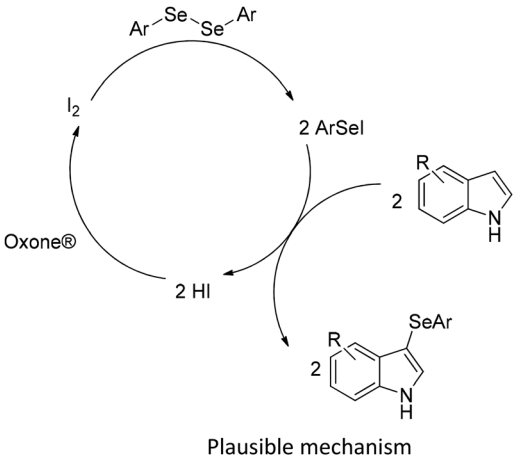
diorganoyl diselenides were tested to evaluate the influence of different groups linked to selenium. Electron-donating or -accepting substituents attached at the *para*-position of the aromatic ring of the diselenide did not affect the performance and the corresponding 3-selenylindoles **3l–n** were obtained in good yields. Notably, the presence of acidic hydrogen, such as in the case of the carboxyl group at the *ortho*-position of the diselenide, also did not significantly influence the reaction, furnishing the corresponding product **3o** in an acceptable yield. The reaction also worked well with a heterocyclic diselenide, containing pyridine, affording the corresponding 3-selenylindole **3p** in 78% yield. In contrast, when the reaction was carried out using an aliphatic diselenide, such as didodecyl diselenide, the corresponding 3-selenylindole **3q** was obtained in only 28% yield, even after 24 h of reaction. Moreover, no significant changes in the yields were observed when the loading of the catalyst was decreased to 10 mol% or 5 mol% or increased to 40 mol% (Table 2, compound **3q**). In the literature it is reported that aliphatic diselenides are less reactive with respect to aromatic ones for this type of transformation.[9a] In order to expand the substrate scope to other heteroaromatic compounds, the indole was replaced with the pyrazole ring (Table 2). The 4-selenyl-1*H*-pyrazoles **3r–s** were synthesized in acceptable yields. The preparation of 3-sulfenylindoles was further explored using the same conditions. As shown in Table 2, the mono- and bis-sulfenylindoles **3t** and **3t′** were isolated in pure form by column chromatography in equal yields of 28%.

Double sulfenylations of indoles have already been observed in iodine-catalyzed oxidative sulfenylation processes.[19] Furthermore, to clarify the reaction mechanism, a radical trapping experiment was conducted by the addition of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) using indole **1a** and diselenide **2a** under the optimized reaction conditions, but no influence in the formation of product **3a** was observed. This result suggests that radical intermediates are not involved (Scheme 1).

Based on this experimental result and previous relevant studies,[9a,b] a plausible reaction mechanism has been proposed (Scheme 2). Initially, diorganyl diselenide reacts with molecular iodine to produce the electrophilic species arylselenyl iodide (ArSeI). Subsequently, the Friedel–Crafts reaction of the indole with the electrophilic species $ArSe^+$ provides the desired 3-selenylindole, with concomitant formation of HI. Finally, HI is oxidized by Oxone® to regenerate molecular iodine, thus completing the catalytic cycle.



Scheme 1 Control experiment.



Scheme 2 Plausible mechanism.

Moreover, with the aim of synthesizing new types of selenyl derivatives as potential inhibitors of human carbonic anhydrase (hCA), we sought to exploit this C(sp^2)–H bond selenylation reaction with a diselenide containing a sulfonamide moiety. As highlighted in Table 3, novel 3-selenylindoles were synthesized employing 4,4′-diselane diyldibenzenesulfonamide (**2i**), which was prepared according to the literature.[15a] These molecules contain three bioactive cores, indole, selenium, and sulfonamide, which are multivalent molecules[20] that may improve potency and selectivity when compared with the monovalent entity. Mono and di-substituted indoles containing various electron-donating or electron-withdrawing groups at different positions were employed (Table 3).

Halides (**4b–e**, and **h**) or methoxy (**4f**), alkyl (**4g–4h**), cyano (**4i**), ester (**4j**) and amide (**4k**) groups at the C5, C4 and C2 positions were well tolerated, and the *N*-methyl protected indole **4l** was successfully employed. It is important to note that these densely functionalized compounds offer the opportunity for further elaboration, allowing the expansion of the range of possible derivatives.

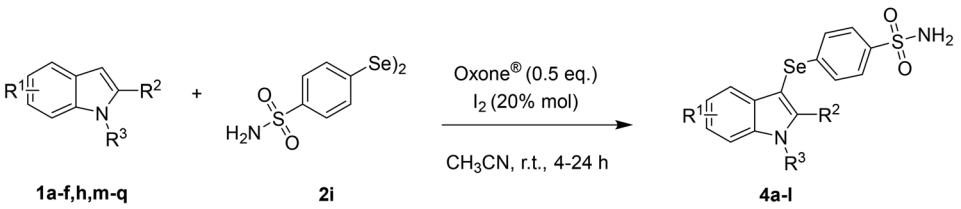
Biological activities

All 3-selenylindoles containing benzensulfonamides **4a–l** were tested *in vitro* for their inhibitory activity towards the physiologically relevant hCA isoforms I, II, IX, and XII using the stopped-flow carbon dioxide hydration assay,[21] after a period of 15 min of incubation of the enzyme and inhibitor solutions. Their activities were compared with that of the standard CAI acetazolamide **AAZ** (Table 4).

The following preliminary structure–activity relationship (SAR) may be noted from the inhibition data shown in Table 4.

(i) The ubiquitous cytosolic hCA I was inhibited by compounds **4a**, **4c**, **4e**, **4i**, **4k**, and **4l**, each with inhibitory constants (K_i) in the nanomolar range (41.0 nM to 80.8 nM), which were lower than that of **AAZ**. Notably, compound **4d**, with a bromine atom at position C5 displayed a significantly

Table 3 Selenylation of indoles with diselenide containing a benzensulfonamide moiety



1a-f,h,m-q 2i 4a-l

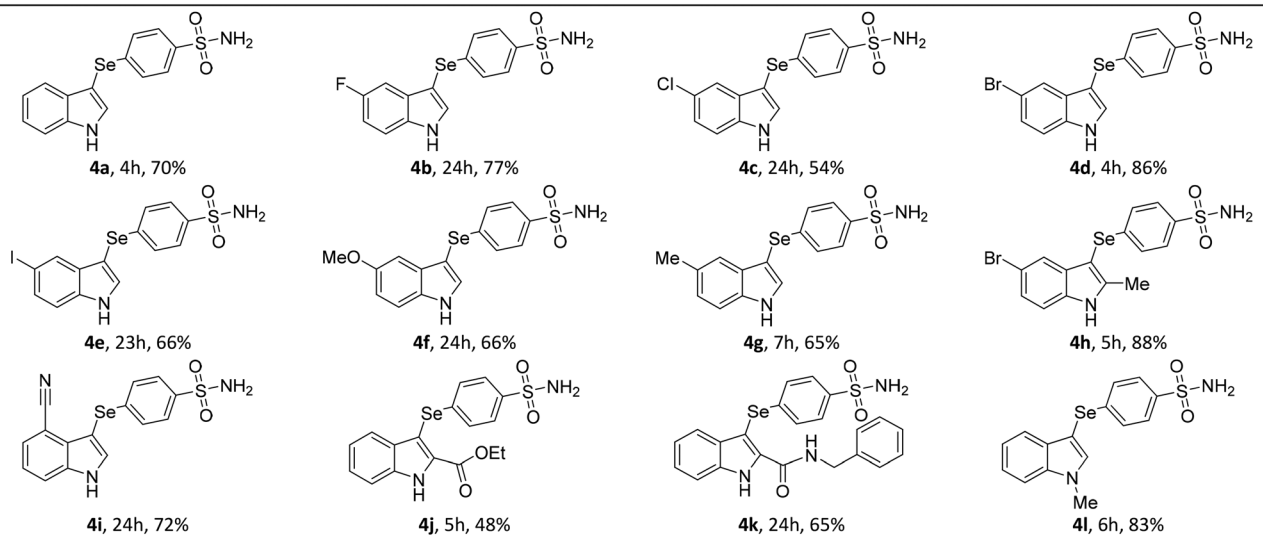


Table 4 Inhibition data of human CA isoforms I, II, IX, and XII with compounds **4a–l** and **AAZ** using a stopped-flow CO_2 hydrase assay[21]

K_i [a] (nM)				
Compound	hCA I	hCA II	hCA IX	hCA XII
4a	73.6	23.6	3.1	6.8
4b	491.9	59.1	2.9	451.3
4c	59.9	43.1	24.0	60.5
4d	7356	948.2	25.4	92.5
4e	65.0	6.9	69.6	32.3
4f	519.7	187.2	14.6	52.2
4g	467.7	83.9	2.1	367.3
4h	573.4	6.2	20.8	87.3
4i	51.1	37.2	17.2	68.8
4j	8488	6915	77.1	323.7
4k	80.8	46.2	24.2	9.8
4l	41.0	6.0	24.5	70.0
AAZ	250	12.1	25.8	5.7

[a] Mean from three different assays, *via* a stopped-flow technique (errors are in the range of ±5–10% of the reported values).

lower potency with a K_i of 7356 nM. Conversely, introducing a methyl group at the position C2, as seen in compound 4h, enhanced the potency by 12 fold (K_i 573.4 nM). The presence of an ethyl ester at position C2 in the indole scaffold, as in compound **4j**, resulted in a high inhibitory constant with a K_i of 8488 nM, indicating a detrimental effect on activity.

(ii) The dominant cytosolic human isoform hCA II was effectively inhibited by compounds **4e**, **4h**, and **4l**, all of which exhibited inhibitory constants in the nanomolar range (K_i 6.0 to 6.9 nM), lower than that of **AAZ**. Notably, the introduction of a methyl group at position C2 in compound **4h** significantly enhanced its inhibitory potency by two orders of magnitude compared to compound **4d** (K_i 6.2 nM *versus* 948.2 nM, respectively), without this moiety, and also improved its selectivity for this isoform. Another compound demonstrating selectivity for hCA II was **4l** (K_i = 6.0 nM), which had a methyl group at position N-1 of the indole scaffold. Conversely, the presence of an ethyl ester at position C2, as in the previous case, resulted in poor inhibitory activity towards this isoform (K_i = 6915 nM).

(iii) All the evaluated compounds effectively inhibited the transmembrane tumor-associated hCA IX, with K_is in the nanomolar range spanning from 2.1 nM to 77.1 nM. Simple substitutions on the indole ring significantly influenced selectivity. Compounds **4b** and **4g**, which contain a fluoride and a methyl group at position C5 of the indole, demonstrated potent and selective activity towards this isoform, with inhibition constants of 2.9 nM and 2.1 nM, respectively. Notably, a decrease in inhibitory activity towards the isoform hCA IX was observed with progression down the halogen series; the fluorine derivative **4b** exhibited the highest selectivity for isoform IX, with progressively less activity noted with chlorine (**4c**), bromine (**4d**), and iodine (**4e**) substitutions.

(iv) The second transmembrane isoform hCA XII was inhibited by all compounds in the medium nanomolar range (K_is spanning from 6.8 nM to 92.5 nM), except for three compounds, **4b**, **4g**, and **4j** that exhibited high nanomolar inhibition constants (K_is spanning from 323.7 nM to 451.3 nM). Generally, simple substituents at position C5 of the indole scaffold were detrimental to activity compared to the unsubstituted derivative **4a**. Similarly, substitutions at position C2 also generally decreased the activity, with the exception of compound **4k**, which displayed a similar K_i value to **4a** (K_i 9.8 nM and 6.8 nM, respectively). Additionally, substitution at N-1, as in the case of **4l**, proved to be less effective in inhibiting potency than **4a** (K_i 70 nM and 6.8 nM, respectively).

Conclusions

In conclusion, a general alternative methodology for the regioselective synthesis of 3-selenylindoles, which uses Oxone® as the oxidant in the presence of a catalytic amount of iodine in acetonitrile at room temperature, has been reported, through direct C(sp^2)–H bond selenylation. This environmentally benign approach is operationally simple, inexpensive, and compatible with a wide array of substrates. Furthermore, several novel 3-selenylbenzensulfonamide indoles were synthesized and tested as inhibitors of four human carbonic anhydrase (hCA) isoforms of pharmacologic relevance, *i.e.*, hCA I, II, IX, and XII. These isoforms are targeted by drugs for glaucoma (hCA I and II) and anticancer therapies (hCA IX and XII). The 3-selenylbenzensulfonamide indoles **4e**, **4h**, and **4l** demonstrated high and selective inhibition towards the isoform hCA II. Conversely, derivatives **4b** and **4g** showed selective activity towards hCA IX. These findings position 3-selenylbenzensulfonamide indoles as promising initial candidates for the development of more potent and selective hCA-inhibitors.

Experimental section

Chemistry

Commercial reagents and solvents were purchased from Sigma Aldrich, Alfa Aesar or VWR International and used without further purification. The starting products indole carboxamides **1f–1g** and diselenides **2b–2g** and **2i** were prepared according to the literature procedures.[4c,11d,15a,22] Thin layer chromatography (TLC) was performed using 60 F254 (Merck, KGaA, Darmstadt, Germany) silica gel supported on aluminium sheets. Reaction products were purified by column chromatography on Merck 60 (70–230 mesh) silica gel. Yields correspond to isolated compounds. Purity was estimated to be ≥95% based on ^{1}H NMR spectroscopic analysis. NMR experiments were carried out at 25 °C on a Bruker Avance NEO 400 MHz spectrometer equipped with a sample case operating at 400 MHz for ^{1}H NMR and 100.62 MHz for ^{13}C NMR or on a Bruker Avance NEO 600 MHz spectrometer equipped with a Prodigy™BBO-Cryoprobe operating at 600.13 MHz for ^{1}H NMR and 150.90 MHz for ^{13}C NMR in $CDCl_3$, CD_3OD, DMSO-d_6 and CD_3COCD_3. ^{77}Se NMR spectra are referenced to a diphenyl diselenide external standard $(PhSe)_2$ and were recorded at 114 MHz.[23] Coupling constants J are expressed in Hz. The following abbreviations are used to indicate multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet, and brs = broad singlet. High-resolution mass spectrometry (HRMS) measurements were performed using a Synapt G2-Si mass spectrometer (Waters) equipped with an APCI/ESI source and a quadrupole-time-of-flight mass analyzer. The mass spectrometer was operated in the positive ion detection mode. To ensure accurate mass measurements, data were collected in a centroid mode and mass was corrected during acquisition using leucine enkephalin solution as an external reference. The results of the measurements were processed using MassLynx 4.1 software (Waters) incorporated with the instrument. Melting points were determined using a Kofler melting apparatus and values are uncorrected.

General procedure for the synthesis of 3-selenylindoles 3a–q, 4-selenylpyrazoles 3r–s, mono- and bis-sulphenylindoles 3t–3t′, and 3-selenyl-benzensulfonammideindoles 4a–l

The indoles **1a–k** and **m–q** (1 eq., 0.5 mmol) or the pyrazole **1l** (1 eq., 0.5 mmol), the diselenides **2a–g** and **i** (0.5 eq., 0.25 mmol) or disulfide **2h** (0.5 eq., 0.25 mmol), Oxone® (0.5 eq., 0.25 mmol) and iodine (20% mol) were dissolved in 5.0 mL of CH_3CN. The reaction mixture was vigorously stirred at room temperature for the time indicated in Tables 2 and 3. Then the reaction was quenched with a saturated solution of $Na_2S_2O_3$, extracted with ethyl acetate (3 × 10 mL), dried with Na_2SO_4, and filtered and the solvent was evaporated under reduced pressure. The crude mixture was purified by column chromatography on silica gel to obtain the corresponding products. Physical and spectroscopic data of the 3-selenylindoles **3a–q**, 4-selenylpyrazoles **3r–s**, mono- and di-sulphenylindoles **3t–t′**, and 3-selenylindoles bearing benzene solfonamides **4a–l** are reported below. The ^{1}H NMR spectra registered in CD_3OD did not show signals for the exchangeable protons of indoles N**H** and SO_2NH_2. Such protons are visible in DMSO-d_6.

3-(Phenylselanyl)-1*H*-indole (3a).[11a] Compound **3a** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 90 : 10 to light petroleum/ethyl acetate 80 : 20) and afforded as a white solid (mp 135–137 °C, lit.[11a] 134–135 °C) in 70% yield. R_f = 0.51 (PE/EtOAc 8 : 2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ (ppm) = 8.44 (brs, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.50 (d, J = 1.9 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.32–7.10 (m, 7H).

5-Chloro-3-(phenylselanyl)-1*H*-indole (3b).[11a] Compound **3b** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 90 : 10 to light petroleum/ethyl acetate 80 : 20) and afforded as a white solid (mp 109–111 °C, lit.[11a] 112–115 °C) in 51% yield. R_f = 0.33 (PE/EtOAc 8 : 2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ (ppm) = 8.50 (brs, 1H), 7.68 (s, 1H), 7.49 (s, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.30–7.17 (m, 6H).

5-Bromo-3-(phenylselanyl)-1*H*-indole (3c).[11a] Compound **3c** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 90 : 10 to light petroleum/ethyl acetate 80 : 20) and afforded as a white solid (mp 136–138 °C, lit.[11a] 135–138 °C) in 80% yield. R_f = 0.36 (PE/EtOAc 8 : 2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ (ppm) = 8.51 (brs, 1H), 7.76 (s, 1H), 7.46 (d, J = 2.6 Hz, 1H), 7.39–7.09 (m, 7 H).

5-Iodo-3-(phenylselanyl)-1*H*-indole (3d).[11a] Compound **3d** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 90 : 10 to light petroleum/ethyl acetate 80 : 20) and afforded as a white solid (mp 128–131 °C, lit.[11a] 125–128 °C) in 61% yield. R_f = 0.36 (PE/EtOAc 8 : 2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ (ppm) = 8.47 (brs, 1H), 8.00 (s, 1H), 7.53 (d, J = 8.3 Hz, 1H), 7.45 (d, J = 2.2 Hz, 1H), 7.29–7.10 (m, 6H).

5-Methoxy-3-(phenylselanyl)-1*H*-indole (3e).[11a] Compound **3e** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 90 : 10 to light petroleum/ethyl acetate 80 : 20) and afforded as a yellow oil in 55% yield. R_f = 0.44 (PE/EtOAc 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ (ppm) = 8.38 (brs, 1H), 7.45 (d, J = 2.2 Hz, 1H), 7.33 (d, J = 8.8 Hz, 1H), 7.26–7.23 (m, 2H), 7.18–7.09 (m, 4H), 6.94 (dd, J = 2.2, 8.8 Hz, 1H), 3.82 (s, 3H).

***N*-Benzyl-3-(phenylselanyl)-1*H*-indole-2-carboxamide (3f).** Compound **3f** was purified by column chromatography (eluent: light petroleum/ethyl acetate 95 : 5 to light petroleum/ethyl acetate 85 : 15) and afforded as a white solid (mp 184–187 °C) in 65% yield. R_f = 0.38 (PE/EtOAc 8 : 2); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ (ppm) = 12.30 (brs, 1H), 8.79 (brs, 1H), 7.65–7.38 (m, 2H), 7.37–7.07 (m, 12H), 4.56 (d, J = 5.3 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 160.9, 138.9, 136.1, 134.6, 132.6, 130.4, 129.6 (2C), 129.1 (2C), 128.6 (2C), 127.3 (2C), 127.1, 126.6, 124.6, 121.3, 120.9, 113.1, 96.6, 42.8; ^{77}Se NMR (76.27 MHz, DMSO-d_6): δ (ppm) = 198.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{19}N_2Ose$: 407.0663; found: 407.0673.

***N*-Phenyl-3-(phenylselanyl)-1*H*-indole-2-carboxamide (3g).** Compound **3g** was purified by column chromatography (eluent: light petroleum/ethyl acetate 95 : 5 to light petroleum/ethyl acetate 85 : 15) and afforded as a white solid (mp 224–228 °C) in 48% yield. R_f = 0.58 (PE/EtOAc 8 : 2); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ (ppm) = 12.44 (brs, 1H) 10.38 (brs, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.37 (t, J = 7.5 Hz, 2H), 7.30 (dt, J = 1.1, 7.0 Hz, 1H), 7.23–7.07 (m, 7H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 159.3, 138.5, 136.4, 135.1, 132.7, 130.2, 129.7 (2C), 129.3 (2C), 129.2 (2C), 126.6, 124.9, 124.3, 121.4, 120.9, 119.8 (2C), 113.1, 97.9; ^{77}Se NMR (76.27 MHz, DMSO-d_6): δ (ppm) = 204.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{17}N_2OSe$ 393.0506; found: 393.0516.

3-(Phenylselanyl)-1*H*-indole-4-carbonitrile (3h).[11a] Compound **3h** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 90 : 10 to light petroleum/ethyl acetate 80 : 20) and afforded as a yellow solid (mp 165–167 °C, lit.[11a] 166–168 °C) in 79% yield. R_f = 0.14 (PE/EtOAc 8 : 2); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C):[11a] δ (ppm) = 12.27 (brs, 1H), 7.99 (d, J = 2.2 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 7.3 Hz, 1H), 7.30 (t, J = 7.9 Hz, 1H), 7.22–7.10 (m, 5H).

3-Methyl-2-(phenylselanyl)-1*H*-indole (3i).[8c] Compound **3i** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 95 : 5 to light petroleum/ethyl acetate 90 : 10) and afforded as a white solid (mp 96–98 °C, lit.[8c] 97–98 °C) in 28% yield. R_f = 0.72 (PE/EtOAc 8 : 2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ (ppm) = 8.47 (brs, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.43–7.05 (m, 8H), 2.46 (s, 3H).

1-Acetyl-3-(phenylselanyl)-1*H*-indole (3k). Compound **3k** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 95 : 5) and afforded as a yellow oil in 5% yield. R_f = 0.46 (PE/EtOAc 9 : 1); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ (ppm) = 8.48 (d, J = 7.6 Hz, 1H), 7.72 (s, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.36–7.32 (m, 2H), 7.31 (t, J = 7.6 Hz, 1H), 7.23–7.18 (m, 3H), 2.60 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 163.2, 136.0, 131.7, 131.3, 130.9, 129.9 (2C), 129.3 (2C), 126.5, 125.9, 124.3, 120.7, 116.7, 116.6, 106.9, 23.9; ^{77}Se NMR (114 MHz, $CDCl_3$): δ (ppm) = 230.9.

3-[(4-Methoxyphenyl)selanyl]-1*H*-indole (3l).[11a] Compound **3l** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 90 : 10 to light petroleum/ethyl acetate 85 : 15) and afforded as a white solid (mp 114–112 °C, lit.[11a] 113–115 °C) in 55% yield. R_f = 0.44 (PE/EtOAc 8 : 2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ (ppm) = 8.37 (brs, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.45–7.38 (m, 2H), 7.34–7.14 (m, 4H), 6.79–6.68 (m, 2H), 3.75 (s, 3H).

3-[(4-Methylphenyl)selanyl]-1*H*-indole (3m).[11a] Compound **3m** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 90 : 10 to light petroleum/ethyl acetate 85 : 15) and afforded as a white solid (mp 108–110 °C, lit.[11a] 105–106 °C) in 72% yield. R_f = 0.70 (PE/EtOAc 8 : 2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ (ppm) = 8.29 (brs, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.43–7.39 (m, 2H), 7.35–7.17 (m, 4H), 7.05–6.95 (m, 2H), 2.29 (s, 3H).

3-[(4-Chlorophenyl)selanyl]-1*H*-indole (3n).[11a] Compound **3n** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 90 : 10 to light petroleum/ethyl acetate 80 : 20) and afforded as a white solid (mp 122–124 °C, lit.[11a] 117–120 °C) in 61% yield. R_f = 0.47 (PE/EtOAc 8 : 2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ (ppm) = 8.47 (brs, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.51 (d, J = 2.2 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.31–7.25 (m, 1H), 7.21–7.07 (m, 5H).

2-[(1*H*-Indol-3-yl)selanyl]-benzoic acid (3o).[11a] Compound **3o** was purified by column chromatography (eluent: from dichloromethane/methanol 98 : 2 to dichloromethane/methanol 96 : 4) and afforded as a brown solid (mp 155–158 °C, lit.[11a] 152–154 °C) in 52% yield. R_f = 0.39 (CH_2Cl_2/MeOH 8 : 2); ^{1}H NMR (400 MHz, CD_3COCD_3, 25 °C): 10.74 (brs, 1H), 8.12 (dd, J = 2.0, 6.9 Hz, 1H), 7.67 (d, J = 2.6 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.26–7.15 (m, 3H), 7.11 (t, J = 7.0 Hz, 1H), 6.96 (dd, J = 1.0, 7.6 Hz, 1H).

3-(Pyridin-4-ylselanyl)-1*H*-indole (3p).[10a] Compound **3p** was purified by column chromatography (eluent: dichloromethane/

methanol 99 : 1) and afforded as a light yellow oil in 78% yield. R_f = 0.53 (CH_2Cl_2/MeOH 8 : 2); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ (ppm) 11.81 (brs, 1H), 8.20 (d, J = 5.6 Hz, 2H), 7.77 (d, J = 2.5 Hz, 1H), 7.51 (d, J = 7.2 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.11–7.05 (m, 3H).

3-(Decylselanyl)-1*H*-indole (3q). Compound **3q** was purified by column chromatography (eluent light petroleum/ethyl acetate 80 : 20) and afforded as a yellow oil in 28% yield. R_f = 0.62 (PE/EtOAc 8 : 2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ (ppm) = 8.18 (brs, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.25 (d, J = 2.3 Hz, 1H), 7.18–7.09 (m, 3H), 2.60 (t, J = 7.4 Hz, 2H), 1.53 (quint, J = 7.2 Hz, 1H), 1.37–1.15 (m, 14H), 0.80 (t, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 136.2, 130.3, 130.0, 122.5, 120.3, 120.2, 111.2, 98.9, 31.8, 30.5, 29.6, 29.5 (2C), 29.3, 29.1, 28.8, 22.6, 14.1; ^{77}Se NMR (76.27 MHz, $CDCl_3$): δ (ppm) = 85.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{28}NSe$: 338.1387; found: 338.1397.

4-(Phenylselanyl)-1*H*-pyrazole (3r).[24] Compound **3r** was purified by column chromatography (eluent light petroleum/ethyl acetate 60 : 40) and afforded as a white solid (mp 92–94 °C; lit[24] 94–95 °C) in 69% yield. R_f = 0.50 (PE/EtOAc 5 : 5); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ (ppm) = 8.18 (brs, 1H), 7.78–7.74 (m, 2H), 7.33–7.25 (m, 2H), 7.24–7.12 (m, 3H).

3-[(4-Chlorophenyl)selanyl]1*H*-pyrazole (3s). Compound **3s** was purified by column chromatography (eluent light petroleum/ethyl acetate 60 : 40) and afforded as a white solid (mp 130–133 °C) in 45% yield. R_f = 0.48 (PE/EtOAc 5 : 5); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ (ppm) = 9.50 (brs, 1H), 7.82–7.70 (m, 2H), 7.23–7.11 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 139.8, 132.2, 131.3, 130.5 (2C), 129.2 (2C), 100.9 (2C); ^{77}Se NMR (76.27 MHz, $CDCl_3$): δ (ppm) = 224.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_9H_8N_2ClSe$: 258.9541; found: 258.9541.

3-(Phenylthio)-1*H*-indole (3t).[9a] Compound **3t** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 90 : 10 to light petroleum/ethyl acetate 85 : 15) and afforded as a white solid (mp 148–150 °C; lit.[9a] 150–151 °C) in 28% yield. R_f (PE/EtOAc 9 : 1) = 0.63; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.41 (brs, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.50–7.45 (m, 2H), 7.29 (t, J = 7.9 Hz, 1H,), 7.24–7.09 (m, 5H), 7.06 (t, J = 7.1 Hz, 1H).

2,3-Bis(phenylthio)-1*H*-indole (3t′).[19] Compound **3t′** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 90 : 10 to light petroleum/ethyl acetate 85 : 15) and afforded as a yellow oil in 28% yield. R_f = 0.45 (PE/EtOAc 9 : 1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ (ppm) = 8.37 (brs, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.31–7.24 (m, 6H), 7.21–7.13 (m, 5H), 7.11–7.07 (m, 1H).

4-(1*H*-Indol-3-ylselanyl)benzenesulfonamide (4a). Compound **4a** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 70 : 30 to light petroleum/ethyl acetate 50 : 50) and afforded as a white solid (mp 185–188 °C) in 70% yield. R_f = 0.40 (PE/EtOAc 1 : 1); ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ (ppm) = 7.64–7.59 (m, 3H), 7.50 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.28–7.25 (m, 2H), 7.21 (t, J = 7.6 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ (ppm) = 11.71 (brs, 1H), 7.72 (d, J = 2.5 Hz, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.22 (d, J = 8.4 Hz, 2H), 7.13 (t, J = 7.9 Hz, 1H), 7.01 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ (ppm) = 141.0, 140.3, 137.0, 132.2, 129.4, 127.4 (2C), 125.9 (2C), 122.1, 119.9, 118.8, 111.5, 94.6; ^{77}Se NMR (76.27 MHz, CD_3OD): δ (ppm) = 223.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}N_2O_2SSe$: 352.9863; found: 352.9868.

4-[(5-Fluoro-1*H*-indol-3-yl)selanyl]benzenesulfonamide (4b). Compound **4b** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 70 : 30 to light petroleum/ethyl acetate 50 : 50) and afforded as a brown solid (mp 62–64 °C) in 77% yield. R_f = 0.31 (PE/EtOAc 1 : 1); ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ (ppm) = 7.65–7.58 (m, 3H), 7.45 (dd, $^4J_{H-F}$ = 4.3, $^3J_{H-H}$ = 8.8 Hz, 1H), 7.26–7.19 (m, 2H), 7.06 (dd, $^4J_{H-H}$ = 2.4, $^3J_{H-F}$ = 9.4 Hz, 1H), 6.95 (dt, $^4J_{H-H}$ = 2.4, $^3J_{H-F}$, $^3J_{H-H}$ = 9.4 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ (ppm) = 158.5 (d, $^1J_{C-F}$ = 233 Hz), 140.6, 140.5, 134.2, 133.6, 130.3 (d, $^3J_{C-F}$ = 10.0 Hz), 127.6 (2C), 126.1 (2C), 112.7 (d, $^3J_{C-F}$ = 9.5 Hz), 110.4 (d, $^2J_{C-F}$ = 26.0 Hz), 103.5 (d, $^2J_{C-F}$ = 24.0 Hz), 94.8 (d, $^4J_{C-F}$ = 4.8 Hz); ^{77}Se NMR (76.27 MHz CD_3OD): δ (ppm) = 224.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{12}N_2O_2SSeF$: 370.9769; found: 370.9771.

4-[(5-Chloro-1*H*-indol-3-yl)selanyl]benzenesulfonamide (4c). Compound **4c** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 80 : 20 to light petroleum/ethyl acetate 50 : 50) and afforded as a white solid (mp 77–80 °C) in 54% yield. R_f = 0.40 (PE/EtOAc 1 : 1); ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ (ppm) = 7.70–7.63 (m, 3H), 7.49 (d, J = 8.6 Hz, 1H), 7.38 (d, J = 1.3 Hz, 1H), 7.31–7.24 (m, 2H), 7.19 (dd, J = 1.6, 8.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ (ppm) = 142.3, 142.1, 137.2, 135.7, 132.5, 129.3 (2C), 127.9 (2C), 127.7, 124.1, 119.9, 114.6, 96.2; ^{77}Se NMR (76.27 MHz, CD_3OD): δ (ppm) = 223.2; HRMS $[M + H]^+$ calcd for $C_{14}H_{12}N_2O_2SSeCl$: 386.9473; found: 386.9475.

4-[(5-Bromo-1*H*-indol-3-yl)selanyl]benzenesulfonamide (4d). Compound **4d** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 60 : 40 to light petroleum/ethyl acetate 40 : 60) and afforded as a white solid (mp 76–79 °C) in 86% yield. R_f = 0.31 (PE/EtOAc 1 : 1); ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ (ppm) = 7.72–7.65 (m, 3H), 7.56 (d, J = 1.2 Hz, 1H), 7.46 (d, J = 8.6 Hz, 1H), 7.34 (dd, J = 1.5, 8.7 Hz, 1H), 7.33–7.28 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ (ppm) = 142.1, 141.7, 137.2, 135.3, 132.8, 128.9 (2C), 127.6 (2C), 126.4, 122.8, 114.8, 114.7, 95.9; ^{77}Se NMR (76.27 MHz CD_3OD): δ (ppm) = 220.9; HRMS $[M + H]^+$ calcd for $C_{14}H_{12}N_2O_2SSeBr$: 430.8968; found: 430.8966.

4-[(5-Iodo-1*H*-indol-3-yl)selanyl]benzenesulfonamide (4e). Compound **4e** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 80 : 20 to light petroleum/ethyl acetate 50 : 50) and afforded as a white solid (mp 164–167 °C) in 66% yield. R_f = 0.38 (PE/EtOAc 1 : 1); ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ (ppm) = 7.74 (d, J = 1.3 Hz, 1H), 7.66–7.60 (m, 2H), 7.56 (s, 1H), 7.44 (dd, J = 1.4, 8.5 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.26–7.22 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ (ppm) = 142.2, 142.1, 137.9, 135.1, 133.8, 132.3,

129.5, 129.2 (2C), 127.8 (2C), 115.4, 95.7, 84.9; ^{77}Se NMR (76.27 MHz CD_3OD): δ = 222.8; HRMS $[M + H]^+$ calcd for $C_{14}H_{12}N_2O_2SSeI$: 478.8829; found: 478.8835.

4-[(5-Methoxy-1*H*-indol-3-yl)selanyl]benzenesulfonamide (4f). Compound **4f** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 80 : 20 to light petroleum/ethyl acetate 50 : 50) and afforded as a brown solid (mp 179–182 °C) in 66% yield. R_f = 0.55 (PE/EtOAc 1 : 1); ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ (ppm) = 7.66–7.59 (m, 2H), 7.56 (s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.29–7.23 (m, 2H), 6.92 (d, J = 2.0 Hz, 1H), 6.88 (dd, J = 2.2, 8.8 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ (ppm) = 156.6, 142.8, 142.1, 134.5, 133.8, 131.9, 129.1 (2C), 127.7 (2C), 114.2, 114.1, 101.9, 95.9, 56.3; ^{77}Se NMR (76.27 MHz, CD_3OD): δ (ppm) = 222.6; HRMS $[M + H]^+$ calcd for $C_{15}H_{15}N_2O_3SSe$: 382.9969; found: 382.9972.

4-[(5-Methyl-1*H*-indol-3-yl)selanyl]benzenesulfonamide (4g). Compound **4g** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 70 : 30 to light petroleum/ethyl acetate 50 : 50) and afforded as a brown solid in 65% yield. R_f = 0.45 (PE/EtOAc 1 : 1); ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ (ppm) = 7.64–7.59 (m, 2H), 7.53 (s, 1H), 7.37 (d, J = 8.3 Hz, 1H), 7.27–7.24 (m, 2H), 7.22 (s, 1H), 7.04 (d, J = 8.3 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ (ppm) = 142.8, 141.8, 136.9, 133.8, 131.2, 130.9, 128.9 (2C), 127.5 (2C), 125.3, 119.9, 112.8, 95.6, 21.7; ^{77}Se NMR (76.27 MHz CD_3OD): δ (ppm) = 220.9; HRMS $[M + H]^+$ calcd for $C_{15}H_{15}N_2O_2SSe$: 367.0019; found: 367.0020.

4-[(5-Bromo-2-methyl-1*H*-indol-3-yl)selanyl]benzenesulfonamide (4h). Compound **4h** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 80 : 20 to light petroleum/ethyl acetate 60 : 40) and afforded as a white solid (mp 126–127 °C) in 88% yield. R_f = 0.36 (PE/EtOAc 1 : 1); ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ (ppm) = 7.53–7.50 (m, 2H), 7.31 (s, 1H), 7.17 (d, J = 8.5 Hz, 1H), 7.11–7.06 (m, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ (ppm) = 144.9, 141.9, 141.7, 136.5, 134.0, 128.8 (2C), 127.6 (2C), 125.6, 122.2, 114.5, 113.8, 94.2, 12.8; ^{77}Se NMR (76.27 MHz CD_3OD): δ (ppm) = 196.9; HRMS $[M + H]^+$ calcd for $C_{15}H_{14}N_2O_2SSeBr$: 444.9125; found: 444.9124.

4-[(4-Cyano-1*H*-indol-3-yl)selanyl]benzenesulfonamide (4i). Compound **4i** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 80 : 20 to light petroleum/ethyl acetate 50 : 50) and afforded as a white solid (mp 239–243 °C) in 72% yield. R_f = 0.36 (PE/EtOAc 7 : 3); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ (ppm) = 12.3 (s, 1H), 7.96 (s, 1H), 7.79 (dd, J = 0.8, 8.3 Hz, 1H), 7.57–7.51 (m, 2H), 7.50 (dd, J = 0.8, 8.3 Hz, 1H), 7.26 (t, J = 8.1 Hz, 1H), 7.25–7.18 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 141.7, 140.5, 137.6, 137.5, 128.1 (2C), 128.0, 127.9 (2C), 126.6, 122.5, 118.1, 117.9, 101.8, 93.3; ^{77}Se NMR (76.27 MHz DMSO-d_6): δ (ppm) = 233.2; HRMS $[M + H]^+$ calcd for $C_{15}H_{12}N_3O_2SSe$: 377.9815; found: 377.9822.

Ethyl-3-{[4-(aminosulfonyl)phenyl]selanyl}-1*H*-indole-2-carboxylate (4j). Compound **4j** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 80 : 20 to light petroleum/ethyl acetate 50 : 50) and afforded as a white solid (mp 126–127 °C) in 48% yield. R_f = 0.35 (PE/EtOAc 1 : 1); ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ (ppm) = 7.54–7.53 (m, 2H), 7.52 (d, J = 8.3 Hz, 1H), 7.49 (d, J = 8.2 Hz, 1H), 7.33–7.25 (m, 3H), 7.11 (t, J = 7.2 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ (ppm) = 164.8, 144.6, 143.5, 140.8, 133.9, 133.4, 132.3 (2C), 129.9 (2C), 129.2, 125.0, 124.7, 116.2, 106.1, 64.7, 17.0; ^{77}Se NMR (76.27 MHz, CD_3OD): δ (ppm) = 255.3; HRMS $[M + H]^+$ calcd for $C_{17}H_{17}N_2O_4SSe$: 425.0074; found: 425.0076.

3-{[4-(Aminosulfonyl)phenyl]selanyl}-*N*-benzyl-1*H*-indole-2-carboxamide (4k). Compound **4k** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 75 : 25 to light petroleum/ethyl acetate 40 : 60) and afforded as a white solid (mp 163–167 °C) in 65% yield. R_f = 0.36 (PE/EtOAc 1 : 1); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ (ppm) = 12.48 (brs, 1H), 8.61 (brs, 1H), 7.70–7.58 (m, 2H), 7.53 (d, J = 7.8 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.39–7.17 (m, 11H), 7.17–7.07 (m, 1H), 4.53 (d, J = 4.6, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 160.9, 142.0, 139.0, 138.4, 136.2, 135.4, 130.1, 128.6 (2C), 128.5 (2C), 127.3 (2C), 127.1, 126.7 (2C), 124.7, 121.5, 120.6, 113.2, 95.4, 42.8; ^{77}Se NMR (76.27 MHz DMSO-d_6): δ (ppm) = 217.2; HRMS $[M + H]^+$ calcd for $C_{22}H_{20}N_3O_3SSe$: 486.0391; found: 486.0396.

4-[(1-Methyl-1*H*-indol-3-yl)selanyl]benzenesulfonamide (4l). Compound **4l** was purified by column chromatography (eluent: from light petroleum/ethyl acetate 80 : 20 to light petroleum/ethyl acetate 60 : 40) and afforded as a white solid (mp 159–161 °C) in 83% yield. R_f = 0.40 (PE/EtOAc 1 : 1); ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 7.63–7.58 (m, 2H), 7.52 (s, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.31–7.22 (m, 3H), 7.12 (t, J = 8.0 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ = 140.8, 140.4, 137.7, 136.1, 130.0, 127.4 (2C), 125.9 (2C), 122.1, 120.1, 119.1, 109.6, 93.6, 31.7; ^{77}Se NMR (76.27 MHz CD_3OD): δ = 222.71; HRMS $[M + H]^+$ calcd for $C_{15}H_{15}N_2O_2SSe$: 367.0019; found: 367.0028.

Biological assay

Carbonic anhydrase inhibition. An Applied Photophysics stopped-flow instrument was used to assay the CA-catalyzed CO_2 hydration activity.[21] Phenol red (at a concentration of 0.2 mM) was used as the indicator, working at the absorbance maximum of 557 nm, with 20 mM Hepes (pH 7.4) as the buffer, and 20 mM Na_2SO_4 (to maintain constant ionic strength), following the initial rates of the CA-catalyzed CO_2 hydration reaction for a period of 10–100 s. The CO_2 concentrations ranged from 1.7 to 17 mM for the determination of the kinetic parameters and inhibition constants.[14a] Enzyme concentrations ranged between 5 and 12 nM. For each inhibitor, at least six traces of the initial 5–10% of the reaction were used to determine the initial velocity. The uncatalyzed rates were determined in the same manner and subtracted from the total observed rates. Stock solutions of the inhibitor (0.1 mM) were prepared in distilled–deionized water and dilutions up to 0.01 nM were done thereafter with the assay buffer. Inhibitor and enzyme solutions were preincubated together for 15 min at room temperature prior to the assay to allow for the for-

mation of the E–I complex. The inhibition constants were obtained by non-linear least-squares methods using PRISM 3 and the Cheng–Prusoff equation, as reported earlier, and represent the mean from at least three different determinations. All CA isoforms were recombinant proteins obtained in house, as reported earlier.[25–27]

Author contributions

Conceptualization, C. S., F. M., and L. B.; methodology, M. P., G. P., and L. B.; validation, A. A., M. P., and L. B.; formal analysis, M. P., A. A., and L. B.; investigation, M. P., A. A., R. G., and A. J. H.; resources, C. S.; data curation, M. P. and L. B.; writing—original draft preparation, A. A. and L. B.; writing—review and editing, G. P., E. J. L., F. M., C. S., C. T. S., and L. B.; supervision, F. M. and L. B.; and funding acquisition, C. S., C. T. S., and L. B. All authors have read and agreed to the published version of the manuscript.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research was funded by the University of Perugia, Fondo per il sostegno della Ricerca di Base 2018, Project "Sviluppo di metodologie innovative per la sintesi efficiente di composti eterociclici, molecole drug-like e intermedi sintetici ad alto valore aggiunto". The work was undertaken as part of the scientific activity of the international multidisciplinary "SeS Redox and Catalysis" network and National Interuniversities Consortium C.I.N.M.P.I.S.

References

1 For selected reviews on N-heteroaromatic compounds in medicinal chemistry, see: (*a*) O. Ebenezer, M. A. Jordaan, G. Carena, T. Bono, M. Shapi and J. A. Tuszynski, *Int. J. Mol. Sci.*, 2022, **23**, 8117; (*b*) M. M. Heravi and V. Zadsirjana, *RSC Adv.*, 2020, **10**, 44247.

2 For selected reviews on the pharmacological importance of indoles, see: (*a*) A. Kumari and R. K. Singh, *Bioorg. Chem.*, 2019, **89**, 103021; (*b*) N. Chadha and O. Silakari, *Eur. J. Med. Chem.*, 2017, **134**, 159; (*c*) N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma and E. H. Choi, *Molecules*, 2013, **18**, 6620.

3 (*a*) W. Hou, H. Dong, X. Zhang, Y. Wang, L. Su and H. Xu, *Drug Discovery Today*, 2022, **27**, 2268; (*b*) H. Chai, S.-Q. Zhang, H. Bai, J. Li, Y. Wang, J. Sun, E. Wen, J. Zhang and M. Xin, *Eur. J. Med. Chem.*, 2021, **223**, 113621; (*c*) W. Hou and H. Xu, *J. Med. Chem.*, 2022, **65**, 4436; (*d*) Y. Wu, B. Li, L. Ying, Y. Chen, Y. Zhang, C. Hu, Y. Zhang, L. Yi, W. Xue, S. Huang and Z. Song, *J. Med. Chem.*, 2024, **67**(9), 7585; (*e*) C. Morán-Serradilla, D. Plano, C. Sanmartín and A. K. Sharma, *J. Med. Chem.*, 2024, **67**(10), 7759.

4 (*a*) W. Ali, R. Benedetti, J. Handzlik, C. Zwergel and C. Battistelli, *Drug Discovery Today*, 2021, **26**, 256; (*b*) F. Mangiavacchi, P. Botwina, E. Menichetti, L. Bagnoli, O. Rosati, F. Marini, S. F. Fonseca, L. Abenante, D. Alves, A. Dabrowska, A. Kula-Pacurar, D. Ortega-Alarcon, A. Jimenez-Alesanco, L. Ceballos-Laita, S. Vega, B. Rizzuti, O. Abian, E. J. Lenardão, A. Velazquez-Campoy, K. Pyrc, L. Sancineto and C. Santi, *Int. J. Mol. Sci.*, 2021, **22**, 7048; (*c*) L. Sancineto, A. Mariotti, L. Bagnoli, F. Marini, J. Desanctis, N. Iraci, C. Santi, C. Pannecouque and O. Tabarrini, *J. Med. Chem.*, 2015, **58**, 960; (*d*) B. M. Viera, S. Thurow, M. da Costa, A. M. Casaril, M. Domingues, R. F. Schumacher, G. Perin, D. Alves, L. Savegnago and E. J. Lenardão, *Asian J. Org. Chem.*, 2017, **6**, 1635; (*e*) D. de Souza, D. O. C. Mariano, F. Nedel, E. Schultze, V. F. Campos, F. Seixas, R. S. Da Silva, T. S. Munchen, V. Ilha, L. Dornelles, A. L. Braga, J. B. T. Rocha, T. Collares and O. E. D. Rodrigues, *J. Med. Chem.*, 2015, **58**, 3329.

5 (*a*) Z. Y. Wen, J. W. Xu, Z. W. Wang, H. Qi, Q. L. Xu, Z. S. Bai, Q. Zhang, K. Bao, Y. L. Wu and W. G. Zhang, *Eur. J. Med. Chem.*, 2015, **90**, 184; (*b*) Q. Guan, C. Han, D. Zuo, M. Zhai, Z. Li, Q. Zhang, Y. Zhai, X. Jiang, K. Bao, Y. Wu and W. Zhang, *Eur. J. Med. Chem.*, 2014, **87**, 306.

6 P. T. Birmann, F. S. S. Sousa, D. H. de Oliveira, M. Domingues, B. M. Vieira, E. J. Lenardão and L. Savegnago, *Eur. J. Pharmacol.*, 2018, **827**, 71.

7 (*a*) A. M. Casaril, M. T. Igniasiak, C. Y. Chuang, B. Viera, N. B. Padilha, L. Carrol, E. J. Lenardão, L. Savegnano and M. J. Davies, *Free Radicals Biol. Med.*, 2017, **113**, 395.

8 (*a*) D. Luo, G. Wu, H. Yang, M. Liu, W. Gao, X. Huang, J. Chen and H. Wu, *J. Org. Chem.*, 2016, **81**, 4485; (*b*) Y. Cao, J. Liu, F. Liu, L. Jiang and W. Yi, *Org. Chem. Front.*, 2019, **6**, 825; (*c*) E. Q. Luz, D. Seckler, J. S. Araújo, L. Angst, D. B. Lima, E. A. M. Rios, R. R. Ribeiro and D. S. Rampon, *Tetrahedron*, 2019, **75**, 1258; (*d*) T. Benchawan, J. Maneewong and R. Saeeng, *ChemistrySelect*, 2023, **8**, e202301988; (*e*) E. A. M. Rios, C. M. B. Gomes, G. L. Silverio, E. Q. Luz, S. Ali, C. D. R. M. D'Oca, B. Albach, R. B. Campos and D. S. Rampon, *RSC Adv.*, 2023, **13**, 914.

9 (*a*) J. B. Azeredo, M. Godoi, G. M. Martins, C. C. Silveira and A. L. Braga, *J. Org. Chem.*, 2014, **79**, 4125; (*b*) H. Li, X. Wang and J. Yan, *Appl. Organomet. Chem.*, 2017, **31**, e3864; (*c*) Y. H. Wang, Y. Q. Zhang, C. F. Zhou, Y. Q. Jiang, Y. Xu, X. Zeng and G. Q. Liu, *Org. Biomol. Chem.*, 2022, **20**, 5463; (*d*) J. Rafique, S. Saba, M. S. Franco, L. Bettanin,

A. R. Schneider, L. T. Silva and A. L. Braga, *Chem. – Eur. J.*, 2018, **24**, 4173; (*e*) J. R. Menezes, M. M. Gularte, F. C. dos Santos, J. A. Roehrs and J. B. Azeredo, *Tetrahedron Lett.*, 2023, **120**, 154446; (*f*) S.-Q. Chen, Q.-M. Wang, P.-C. Xu, S.-P. Ge, P. Zhong and X.-H. Zhang, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2016, **191**, 100.

10 (*a*) Y. Yu, Y. Zhou, Z. Song and G. Liang, *Org. Biomol. Chem.*, 2018, **16**, 4958; (*b*) N. L. Ferreira, J. B. Azeredo, B. L. Fiorentin and A. L. Braga, *Eur. J. Org. Chem.*, 2015, 5070; (*c*) S. K. Bhunia, P. Das and R. Jana, *Org. Biomol. Chem.*, 2018, **16**, 9243.

11 (*a*) S. Saba, J. Rafique, M. S. Franco, A. R. Schneider, L. Espíndola, D. O. Silva and A. L. Braga, *Org. Biomol. Chem.*, 2018, **16**, 880; (*b*) V. Rathore and S. Kumar, *Green Chem.*, 2019, **21**, 2670; (*c*) I. D. Lemir, W. D. Castro-Godoy, A. A. Hereida, L. C. Schimidtand and J. E. Argüello, *RSC Adv.*, 2019, **9**, 22685; (*d*) Q. B. Zhang, Y. L. Ban, P. F. Yuan, S. J. Peng, J. G. Fang, L. Z. Wu and Q. Liu, *Green Chem.*, 2017, **19**, 5559.

12 X. Zhang, C. Wang, H. Jiang and L. Sun, *Chem. Commun.*, 2018, **54**, 8781.

13 (*a*) M. Palomba, I. F. Coelho Dias, M. Cocchioni, F. Marini, C. Santi and L. Bagnoli, *Molecules*, 2023, **28**, 6026; (*b*) M. Palomba, L. Sancineto, F. Marini, C. Santi and L. Bagnoli, *Tetrahedron*, 2018, **74**, 7156; (*c*) M. Palomba, S. Pompei, L. Roscini and L. Bagnoli, *ARKIVOC*, 2019, **part ii**, 163; (*d*) M. Palomba, E. Vinti, F. Marini, C. Santi and L. Bagnoli, *Tetrahedron*, 2016, **72**, 7059; (*e*) L. Bagnoli, in *Targets in Heterocyclic System*, ed. O. A. Attanasi, P. Merino and D. Spinelli, 2019, vol. 23, ch. 11, pp. 220–236.

14 (*a*) C. T. Supuran, *Nat. Rev. Drug Discovery*, 2008, **7**, 168; (*b*) A. Nocentini and C. T. Supuran, *Expert Opin. Drug Discovery*, 2019, **14**, 1175.

15 (*a*) A. Angeli, D. Tanini, A. Capperucci and C. T. Supuran, *ACS Med. Chem. Lett.*, 2017, **8**, 1213; (*b*) A. Angeli, D. Tanini, C. Viglianisi, L. Panzella, A. Capperucci, S. Menichetti and C. T. Supuran, *Bioorg. Med. Chem.*, 2017, **25**, 2518; (*c*) D. Tanini, A. Capperucci, M. Scopelliti, A. Milaneschi, A. Angeli and C. T. Supuran, *Bioorg. Chem.*, 2019, **89**, 102984; (*d*) A. Angeli, L. di Cesare Mannelli, E. Trallori, T. S. Peat, C. Ghelardini, F. Carta and C. T. Supuran, *ACS Med. Chem. Lett.*, 2018, **9**, 462; (*e*) A. Angeli, L. di Cesare Mannelli, E. Lucarini, T. S. Peat, C. Ghelardini and C. T. Supuran, *Eur. J. Med. Chem.*, 2018, **154**, 210; (*f*) A. Angeli, D. Tanini, T. S. Peat, L. Di Cesare Mannelli, G. Bartolucci, A. Capperucci, C. Ghelardini, C. T. Supuran and F. Carta, *ACS Med. Chem. Lett.*, 2017, **8**, 963; (*g*) A. Angeli, F. Carta, G. Bartolucci and C. T. Supuran, *Bioorg. Med. Chem.*, 2017, **25**, 3567; (*h*) A. Angeli, D. Tanini, A. Nocentini, A. Capperucci, M. Ferraroni, P. Gratteri and C. T. Supuran, *Chem. Commun.*, 2019, **55**, 648.

16 H. A. Goulart, D. R. Araujo, F. Penteado, R. G. Jacob, G. Perin and E. J. Lenardão, *Molecules*, 2021, **26**, 7523.

17 H. Hussain, I. R. Green and I. Ahmed, *Chem. Rev.*, 2013, **113**, 3329.

18 P. Kumar and A. Bhalla, *Top. Curr. Chem.*, 2024, **382**(2), 12.

19 H. Zhang, X. Bao, Y. Song, J. Qu and B. Wang, *Tetrahedron*, 2015, **71**, 8885.

20 S.-K. Choi, *Synthetic Multivalent Molecules: Concepts and Biomedical Applications*, Wiley Interscience, Hoboken NJ, 2004.

21 R. G. Khalifah, *J. Biol. Chem.*, 1971, **246**, 2561.

22 (*a*) S. K. Sharma, A. K. Mandadapu, B. Kumar and B. Kundu, *J. Org. Chem.*, 2011, **76**, 6798; (*b*) A. Krief and M. Derock, *Synlett*, 2005, 1012; (*c*) K. B. Sharpless and M. W. Young, *J. Org. Chem.*, 1975, **40**, 947; (*d*) D. Singh, A. M. Deobald, L. R. S. Camargo, G. Tabarelli, O. E. D. Rodrigues and A. L. Braga, *Org. Lett.*, 2010, **12**, 3288.

23 R. H. Bartz, P. S. Hellwig, G. Perin, L. E. B. Iarocz, A. Madabeni, L. Orian and M. S. Silva, *New J. Chem.*, 2024, **48**, 2971.

24 A. L. Belladona, R. Cervo, D. Alves, T. Barcellos, R. Cargnelutti and R. F. Schumacher, *Tetrahedron Lett.*, 2020, **61**, 152035.

25 A. Angeli, L. Micheli, R. Turnaturi, L. Pasquinucci, C. Parenti, V. Alterio, A. Di Fiore, G. De Simone, S. M. Monti, F. Carta, L. Di Cesare Mannelli, C. Ghelardini and C. T. Supuran, *Eur. J. Med. Chem.*, 2023, **260**, 115783.

26 A. Angeli, E. Trallori, F. Carta, L. Di Cesare Mannelli, C. Ghelardini and C. T. Supuran, *ACS Med. Chem. Lett.*, 2018, **9**, 947.

27 D. Tanini, A. Capperucci, M. Ferraroni, F. Carta, A. Angeli and C. T. Supuran, *Eur. J. Med. Chem.*, 2020, **185**, 111811.

