Synthesis and anti-HIV Activity of New Benzimidazole, Benzothiazole and Carbohyrazide Derivatives of the anti-Inflammatory Drug Indomethacin

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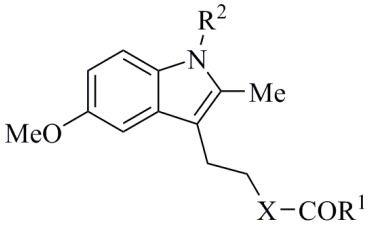
There is an urgent need for the design and development of new and safer drugs for the treatment of HIV infection, active against the currently resistant viral strains. New derivatives of the non-steroidal anti-inflammatory drug indomethacin bearing benzimidazoles, benzothiazole, purine and pyridine residues **8** – **13** were synthesized with the aim of developing new non-nucleoside reverse transcriptase inhibitors (NNRTIs). Alternatively, new imine analogs **16** – **20** were synthesized from condensation of indomethacinyl hydrazide **15**, prepared from the ester **14**, with various ketone precursors. Treatment of **15** with phenyl isothiocyanate or triethyl orthoformate afforded the phenylcarbonothioyl and the oxadiazole derivatives **21** and **22**, respectively. The new compounds were assayed against HIV-1 and HIV-2 in MT-4 cells. Compounds **9** and **10** were the most active in inhibiting HIV-2 and HIV-1, respectively, with $EC_{50} \geq 17.60\ \mu g\,mL^{-1}$ and $> 1.15\ \mu g\,mL^{-1}$ (therapeutic indexes (SI) of ≥ 3 and < 1, respectively), and are leading candidates for further development.

Key words: Anti-HIV Activity, Benzimidazole, Indomethacin, Non-nucleoside Reverse Transcriptase Inhibitors

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are important therapeutic agents for the treatment of pain and inflammation related to a large variety of pathologies [1]. NSAIDs inhibit the cyclooxgenase (COX) activity resulting in decreased synthesis of prostaglandin, leukotriene and thromboxane precursors. Several reports indicate that NSAIDs can prevent the development of various human tumors, including colon, breast, lung, gastric, and esophageal neoplasias [2].

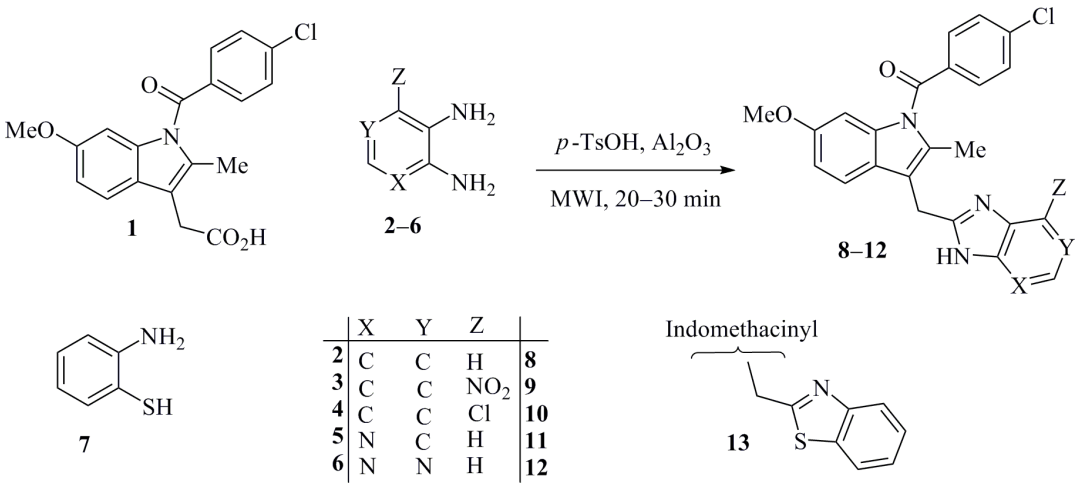
Indomethacin is a drug which belongs to the NSAID drug class, acts by inhibiting isoforms of cyclooxygenase 1 and 2, having activity to treat inflammatory rheumatoid diseases and relieve acute pain. Rogers *et al.* [3] reported the strategy of addressing the stimulation of the immune system which has been effective in reducing Alzheimer's disease progression in clinical trials related to the cyclooxygenase inhibitor indomethacin, which rapidly and efficiently penetrates the blood-brain barrier. However, indomethacin can cause severe adverse gastrointestinal effects in humans and animals, particularly when administered orally [4].



X = O or NH
R^1 = alkyl or aryl
R^2 = 4-Cl-(C_6H_4)-CO or 4-Br-(C_6H_4)-CO

Fig. 1.

Recently, Kalgutkar *et al.* [5] have synthesized some indolyl esters and amides related to indomethacin as selective COX-2 inhibitors (Fig. 1). Furthermore, Camaco-Camaco *et al.* [6] have reported the synthesis and *in vitro* cytotoxicity of various indomethacin-derived *n*-alkyl-tin complexes, while Jones *et al.* [7] reported the cytotoxic activity of a new indomethacin



	X	Y	Z	
2	C	C	H	**8**
3	C	C	NO_2	**9**
4	C	C	Cl	**10**
5	N	C	H	**11**
6	N	N	H	**12**

Scheme 1. Synthesis of benzimidazoles **8**–**10**, imidazolo-pyridine **11**, purine **12**, and benzothiazole **13** derivatives from indomethacin (**1**) and various arene diamines (**2**–**6**) and 2-aminobenzenethiol (**7**).

analog, 7-(4-chlorobenzoyl)-4,6-dimethoxy-2-methyl-3-phenylindole.

The metal complexes of indomethacin exhibited remarkably potent activity in humans [8]. While aspirin [9], ibuprofen [10], and indomethacin [11] are very weak free radical scavengers for *in vitro* systems, their copper complexes are very efficient free radical scavengers [12]. These drugs are thus expected to circumvent the toxicity of reactive oxygen species generated in the activated microglia. Yi and coworkers [13] reported that the copper complex exhibited higher antibacterial activity than the parent drug whose IC_{50} value was 1.5 and 2.3 times lower than that of indomethacin to *S. aureus* and *E. coli*, respectively. It was indicated that when the copper ion is coupled with indomethacin, the drug is more potent as a bacteriostatic.

On the other hand, benzimidazoles were reported to be potent biological molecules as anti-ulcer, antihypertensive, antiviral, antifungal, anticancer, and antihistaminic agents [14]. Some benzimidazoles have been reported as HIV-1 reverse transcriptase inhibitors, and/or potent DNA gyrase inhibitors, for example thiazolo[3,4-*a*]benzimidazoles (TBZs) and their analogs [15–17] and 1-(2,6-difluorophenyl)-thiazolo-[3,4-*a*]benzimidazole (NSC625487), since they inhibited the replication of various strains of HIV-1 including a zidovudine-resistant strain (G910-6) [18]. Monforte and coworkers [19] have reported the synthesis of new thiazolo[3,4-*a*]benzimidazoles and 2-aryl-1-benzylbenzimidazoles as HIV-1 RT inhibitors.

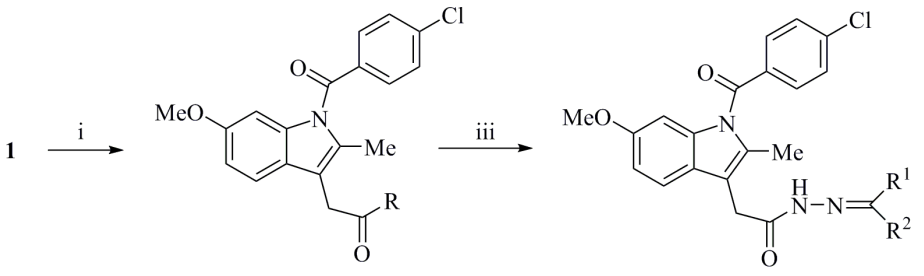
In continuation of our attempts in searching for new anti-HIV agents [20–28] and on the basis of the above mentioned promising biological results, we considered benzimidazoles and their analogs particularly interesting to optimize the synthetic approaches to our antiviral agents. In this study, the anti-inflammatory drug indomethacin [29] has been selected as a main backbone for the synthesis of new benzimidazole and benzothiazole derivatives and their analogs, using the microwave irradiation method.

Results and Discussion

Synthesis

Treatment of indomethacin **1** with the appropriate 1,2-arenediamines **2**–**6** or 2-amino-thiophenol (**7**) in the presence of *p*-toluenesulfonic acid (*p*-TsOH) and Al_2O_3 under MW irradiation (20–30 min, 100–150 W) afforded the benzimidazole-bearing indomethacin **8** and the related analogs **9**–**13**, isolated by conventional work-up, in 55–71 % yield (Scheme 1).

The structures of **8**–**13** were assigned on the basis of their ^1H, ^{13}C NMR and mass spectra. They showed similar NMR patterns of aliphatic and aromatic H atoms. Compounds **8**–**13** showed two doublets at higher fields (δ = 7.72–7.65 and 7.51–7.43 ppm), attributed to 2-$H_{arom\text{-}Cl}$, 6-$H_{arom\text{-}Cl}$ and 3-$H_{arom\text{-}Cl}$, 5-$H_{arom\text{-}Cl}$ (J = 6.7–7.0 Hz), respectively. The doublet at δ = 7.66 ppm was assigned to 4-$H_{benzimidazole}$ and 7-$H_{benzimidazole}$ (J = 8.0 Hz). H-4



	R^1	R^2
16		
17	CMe_3	2-Me-5-OMe-C_6H_3
18	Ph	4-OMe-C_6H_4
19	Ph	$C(Me)_2NH_2$
20	Ph	CH_2Ph

Scheme 2. Reagents and conditions: (i) EtOH, H_2SO_4, reflux, 5 h; (ii) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, 8 h; (iii) $R^1R^2C{=}O$, EtOH, reflux, 3 h.

and H-7 of the indole moiety appeared as doublets at δ = 6.95 – 6.82 and 6.76 – 6.59 ppm ($J \sim 9.0$ Hz), while H-7 gave a doublet of doublets in the region δ = 7.02 – 6.84 ppm ($J \sim 9.0$ and ~ 2.5 Hz). The singlets at δ = 3.81 – 3.70 ppm were assigned to OMe groups, while the singlets at δ = 3.75 – 3.64 ppm were attributed to methyl groups at C-2. H-6 of the pyridine residue of **11** appeared as a doublet of doublets at δ = 6.97 ppm (J = 8.8, 2.6 Hz). H-4 and H-5 of the purine moiety of **12** gave doublets at δ = 9.05 and 8.90 ppm (J = 2.2 Hz), respectively. The ^{13}C NMR spectra of **9** – **12** were recorded (Experimental Section), and compound **13** was selected for the ^{13}C NMR analysis. The spectrum showed higher field signals at δ = 168.3 and 166.2 ppm which were assigned to C=O and C-2 of benzothiazole, respectively. The resonances at δ = 156.1 and 154.1 ppm were attributed to C-6 of the indole and to C-3a of the benzothiazole moieties. C-7a and C-2 of the indole appeared at δ = 136.9 and 133.8 ppm, respectively. The signals at δ = 125.6 and 121.9 ppm were assigned to C-5 and C-6 of the benzothiazole, while the signal at δ = 121.9 ppm was assigned to C-4 and C-7 of the same ring. The resonances at δ = 118.9, 118.3, 111.7, and 101.3 ppm were attributed to C-4, C-3a, C-3, C-5, and C-7 of the indole, respectively. The signals at δ = 55.8, 23.5, and 13.4 ppm were assigned to methoxy, methylene and methyl groups. The purine derivative **12** was selected for further spectroscopic analysis. From the gradient-selected HMBC spectrum [30] CH-2 at δ_H = 3.68 ppm showed two heteronuclear $^2J_{C,H}$ correlations: one with C-3 of the indole ring at δ_C = 136.1 ppm and the other with C-2 of the purine ring at δ_C = 148.9 ppm.

Next, other models of indomethacin derivatives bearing imine derivatives *via* an acetohydrazide linkage were prepared, aiming to evaluate their anti-HIV activity. Esterfication of **1** with acidic EtOH afforded the ester **14** (82 %) [31], which was converted into the hydrazide **15** (64 %) [32] on treatment with hydrated hydrazine. Treatment of **15** with various ketones gave the imine derivatives **16** – **20** in 82, 85, 79, 78, and 85 % yield, respectively (Scheme 2).

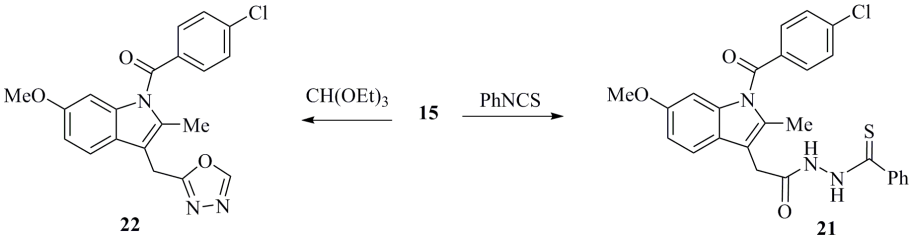
The assignment of protons and carbons of the indomethacin backbone was deduced in comparison to compounds **8** – **12**. The ^1H NMR spectrum of **14** showed a quartet at δ = 3.78 ppm (J = 7.1 Hz) and a triplet at δ = 1.19 ppm, assigned to the ethyl protons of the ester group. The signals had disappeared in the spectrum of **15** and instead, three signals at δ = 10.38, 9.86, and 9.06 ppm were seen, attributed to NH groups. Compounds **16** – **20** showed singlets at δ = 3.68, 3.36, 3.37, 3.47, and 3.44 ppm, assigned to the methylene protons. In the ^{13}C NMR spectra of **14** and **15**, the C=O carbon atoms of the ester and carbohydrazide groups resonated at δ = 170.9 and 170.7 ppm, respectively, while the amide carbon atom resonated at δ = 168.3 ppm. Compounds **16** – **20** showed three resonances at δ = 170.0 – 174.0, 167.9 – 164.8 and 155.9 – 152.9 ppm, attributed to the NHNC=O, C_{amide}=O and C=N carbon atoms, respectively.

Further, treatment of **15** with phenyl isothiocyanate or triethyl orthoformate in boiling EtOH afforded the phenylcarbonothioyl-carbohydrazide **21** and the 1,2,4-

Table 1. *In-vitro* anti-HIV-1[a] and HIV-2[b] activity and cytotoxicity of compounds **8** – **22**.

Entry	HIV-1 (III_B) EC_{50} ($\mu g\,mL^{-1}$)[c]	HIV-2 (ROD) EC_{50} ($\mu g\,mL^{-1}$)[c]	CC_{50} ($\mu g\,mL^{-1}$)[d]	SI[e] (III_B)	SI[e] (ROD)
8	> 54.58	> 54.58	54.58	< 1	< 1
9	> 54.08	≥ 17.60	54.08	< 1	≤ 3
10	> 1.15	> 1.15	1.15	< 1	< 1
11	> 56.15	> 56.15	56.15	< 1	< 1
12	> 67.10	> 67.10	67.10	< 1	< 1
13	> 12.95	> 12.95	12.95	< 1	< 1
14	> 36.13	> 36.13	36.13	< 1	< 1
15	> 96.63	> 96.63	96.63	< 1	< 1
16	> 23.29	> 23.29	23.29	< 1	< 1
17	> 100	> 100	100	< 1	< 1
18	> 66.95	> 66.95	66.95	< 1	< 1
19	> 89.38	> 89.38	89.38	< 1	< 1
20	> 70.08	> 70.08	70.08	< 1	< 1
21	> 68.78	> 68.78	68.78	< 1	< 1
22	> 2.39	> 2.39	2.39	< 1	< 1
Nevirapine	0.050	> 4.00	> 4.00	> 80	< 1
AZT	0.0022	0.00094	> 25	> 11363	> 26596

[a] Anti-HIV-1 activity measured with strain III_B; [b] anti-HIV-2 activity measured with strain ROD; [c] compound concentration required to achieve 50 % protection of MT-4 cells from the HIV-1- and 2-induced cytopathogenic effect; [d] compound concentration that reduces the viability of mock-infected MT-4 cells by 50 %; [e] SI: selectivity index (CC_{50}/EC_{50}).



Scheme 3. Synthesis of indomethacin bearing *N*-(phenylcarbonothioyl)acetohydrazide (**21**) and oxadiazole (**22**) functions.

oxadiazole analogs **22** in 78, and 62 % yield, respectively (Scheme 3). The structures of **21** and **22** were confirmed by their ^1H and ^{13}C NMR spectra. The ^1H NMR spectrum of **21** showed two doublets at δ = 10.02 and 9.60 ppm (J = 4.8 Hz), attributed to NH groups, which disappeared on D_2O exchange. In the ^{13}C NMR spectrum of **21**, the signal at lower field (δ = 187.3 ppm) was assigned to C=S, while the resonances at δ = 171.7 and 165.0 ppm were assigned to NHNC=O and C=O (amide) groups, respectively. In the ^1H NMR spectrum of **22**, 5-H of the oxadiazole moiety appeared as a singlet at δ = 9.34 ppm, while its ^{13}C NMR spectrum showed a signal at δ = 153.0 ppm, assigned to C-5 of the oxadiazole ring. The proton and carbon signals of the indole backbone of **21** and **22** were deduced from a comparison with those of **8** – **12**.

In-vitro anti-HIV assay

Compounds **8** – **21** were tested for their *in vitro* anti-HIV-1 (strain IIIB) and HIV-2 (strain ROD) activity in human T-lymphocyte (MT-4) cells based on the MTT assay [33]. The results are summarized in Table 1, in which the data for Nevirapine (BOE/BIRG587) [34] and azidothymidine (DDN/AZT) [35] were included for comparison. Compound-induced cytotoxicity was also measured in MT-4 cells parallel with the antiviral activity.

Compounds **9** and **10** were found to be the only compounds in the series inhibiting HIV-2 and HIV-1 replication in a cell culture, respectively, which showed EC_{50} values of $\geq 17.60\,\mu g\,mL^{-1}$ and $> 1.15\,\mu g\,mL^{-1}$ with CC_{50} values of $> 54.08\ \mu g\,mL^{-1}$ and $> 1.15\ \mu g\,mL^{-1}$, respectively, resulting in a selectivity index of ≥ 3 and < 1, respectively.

Based on the chemical structure of compounds **9** and **10**, these molecules can be proposed to act as non-nucleoside reverse transcriptase inhibitors (NNRTIs). However, the activity spectrum that is limited to HIV-2 (in case of compound **9**) is completely in contrast with what was observed with NNRTIs.

In conclusion, the above data suggest that substitution of the aromatic ring of the benzimidazole back-

bone by a nitro group would engender the inhibitory activity on HIV-2 replication that is most exceptional, while the substitution with a halogen atom (like chlorine) would enhance the activity of HIV-1.

Experimental Section

General

Melting points are uncorrected and were measured on a Büchi melting point apparatus B-545 (Büchi Labortechnik AG, Switzerland). NMR data were obtained on 400 and 600 MHz (^{1}H) and 150.91 MHz (^{13}C) spectrometers (Avance III, Bruker, Germany) with TMS as internal standard and on the δ scale in ppm. Heteronuclear assignments were verified by ^{1}H-^{13}C COSY, or HMQC experiments. Microanalytical data were obtained with a Vario, Elemental analyzer (Shimadzu, Japan). Mass spectra were recorded on EI (70 eV) and FAB MAT 8200 spectrometers (Finnigan MAT, USA). Microwave-assisted reactions were carried out in a CEM Focused Microwave Synthesis System (100 – 150 W). Silica gel (0.040 – 0.063 mm) used for column chromatography and analytical silica gel TLC plates 60 F254 were purchased from Merck.

*General procedure for the preparation of the indomethacinyl-benzimidazole, -pyridine, -pyrimidine, and -benzothiazole derivatives **6** – **13***

A mixture of indomethacin (**1**) (537 mg, 1.50 mmol) 1,2-arenediamine (1.0 mmol), *p*-toluenesulfonic acid (*p*-TsOH) (10 mg) and Al_2O_3 (20 mg) was thoroughly ground with a pestle in a mortar at r. t. in an open atmosphere, then irradiated in MWI. After the reaction was completed, the mixture was allowed to cool to r. t. and then partitioned between $CHCl_3$ (3 × 15 mL) and a dil. solution of $NaHCO_3$ (15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to dryness. The crude product was purified on a column of SiO_2 (5 g) (eluents: hexane-EtOAc = 3 : 2 or, in gradient, MeOH (0 – 10 %) and $CHCl_3$) to give the desired product.

*(3-((Benzimidazol-2-yl)methyl)-6-methoxy-2-methyl-1H-indol-1-yl)(4-chlorophenyl)methanone (**8**)*

From *o*-phenylenediamine (**2**) (108 mg). Yield: 398 mg (62 %); oil. – ^{1}H NMR ($CDCl_3$): δ = 7.70 (d, 2 H, J = 6.8 Hz, 2-$H_{arom\text{-}Cl}$ + 6-$H_{arom\text{-}Cl}$), 7.66 (d, 2 H, J= 8.0 Hz, 4-$H_{benzimidazole}$ + 7-$H_{benzimidazole}$), 7.51 (d, 2 H, J= 6.8 Hz, 3-$H_{arom\text{-}Cl}$ + 5-$H_{arom\text{-}Cl}$), 7.49 (d, 2 H, J = 8.0 Hz, 5-$H_{benzimidazole}$ + 6-$H_{benzimidazole}$), 7.02 (dd, 1 H, J = 9.0 Hz, 2.8 Hz, 5-H_{indole}), 6.92 (d, 1 H, J = 9.0 Hz, 4-H_{indole}), 6.71 (d, 1 H, J = 2.8 Hz, 7-H_{indole}), 3.81 (s, 3 H, OMe), 3.74 (s, 2 H, CH_2), 2.40 (s, 3 H, Me). – ^{13}C NMR ($CDCl_3$): δ = 168.2 (C=O), 155.9 (6-C_{indole}), 139.1 (4-$C_{arom\text{-}Cl}$ + 2-$C_{benzimidazole}$), 138.9 (3a-$C_{benzimidazole}$+7a-$C_{benzimidazole}$ + 7a-C_{indole}), 135.9 (2-C_{indole}), 131.1, 130.7, 129.0, 128.9, 122.9, 120.5 (C_{arom}), 115.0 (4-$C_{benzimidazole}$), 111.6 (3-C_{indole} + 5-C_{indole}), 101.2 (7-C_{indole}), 55.6 (OMe), 25.2 (CH_2); 13.3 (Me). – HRMS ((+)-ESI): m/z = 479.9074 (calcd. 479.9100 for $C_{25}H_{20}ClN_3O_2$, $[M]^+$).

*(4-Chlorophenyl)(6-methoxy-2-methyl-3-((4-nitrophenyl-1H-benzoimidazol-2-yl)methyl)-1H-indol-1-yl)methanone (**9**)*

From 3-nitrobenzene-1,2-diamine (**3**) (153 mg). Yield: 488 mg (65 %); oil. – ^{1}H NMR ($CDCl_3$): δ = 7.98 – 7.61 (m, 4 H, Ar-H), 7.47 – 7.43 (m, 3 H, Ar-H), 6.97 (dd, 1 H, J = 9.0 Hz, 2.8 Hz, 5-H_{indole}), 6.85 (d, 1 H, J = 9.0 Hz, 4-H_{indole}), 6.71 (d, 1 H, J = 2.6 Hz, 7-H_{indole}), 3.70 (s, 3 H, OMe), 3.75 (s, 2 H, CH_2), 2.37 (s, 3 H, Me). – ^{13}C NMR ($CDCl_3$): δ = 168.3 (C=O), 156.0 (6-C_{indole}), 139.3 (4-$C_{arom\text{-}Cl}$ + 2-$C_{benzimidazole}$), 139.2 (7a-$C_{benzimidazole}$), 136.0 (7a-C_{indole}), 135.9 (2-C_{indole} + 4-$C_{arom-NO2}$), 133.8 (3a-$C_{benzimidazole}$), 131.1, 130.7, 130.6, 129.2, 128.5, 122.1 (C_{arom}), 119.4 (3a-C_{indole} + 4-C_{indole} + 5-$C_{benzimidazole}$), 111.5 (3-C_{indole}), 101.3 (7-C_{indole}), 55.6 (OMe), 25.3 (CH_2), 13.3 (Me). – HRMS ((+)-ESI): m/z = 474.9045 (calcd. 474.9076 for $C_{25}H_{19}ClN_4O_4$, $[M]^+$).

*(3-((4-Chloro-benzimidazol-2-yl)methyl)-6-methoxy-2-methyl-1H-indol-1-yl)(4-chloro-phenyl)methanone (**10**)*

From 3-chlorobenzene-1,2-diamine (**4**) (142 mg). Yield: 475 mg (65 %). – ^{1}H NMR ($CDCl_3$): δ = 7.72 (d, 2 H, J = 6.6 Hz, 2-$H_{arom\text{-}Cl}$ + 6-$H_{arom\text{-}Cl}$), 7.60 (dd, 1 H, J = 6.7 Hz, J = 2.5 Hz, 5-$H_{benzimidazole}$), 7.50 (d, 2 H, J = 6.7 Hz, 3-$H_{arom\text{-}Cl}$ + 5-$H_{arom\text{-}Cl}$), 7.25 (m, 2 H, 5-$H_{benzimidazole}$ + 6-$H_{benzimidazole}$), 6.89 (dd, 1 H, J = 9.0 Hz, 2.8 Hz, 5-H_{indole}), 6.92 (d, 1 H, J = 8.9 Hz, 4-H_{indole}), 6.70 (d, 1 H, J = 2.7 Hz, 7-H_{indole}), 3.71 (s, 3 H, OMe), 3.66 (s, 2 H, CH_2), 2.40 (s, 3 H, Me). – ^{13}C NMR ($CDCl_3$): δ = 168.0 (C=O), 154.6 (6-C_{indole}), 139.2 (4-$C_{arom\text{-}Cl}$ + 7a-$C_{benzimidazole}$), 138.4 (3a-$C_{benzimidazole}$+7a-C_{indole}), 135.5 (2-C_{indole}), 131.0, 130.2, 129.1, 128.6, 122.7, 120.2 (C_{arom}), 113.9 (7-$C_{benzimidazole}$), 111.2 (3-C_{indole} + 5-C_{indole}), 101.0 (7-C_{indole}), 55.5 (OMe), 25.1 (CH_2), 13.3 (Me). – $C_{25}H_{19}Cl_2N_3O_2$: calcd. C 64.66, H 4.12, N 9.05; found C 64.38, H 4.04, N 8.69.

*(3-((3H-Imidazo[4,5-b]pyridin-2-yl)methyl)-6-methoxy-2-methyl-1H-indol-1-yl)(4-chlorophenyl)methanone (**11**)*

From 2,3-diaminopyridine (**5**) (109 mg). Yield: 459 mg (71 %). – ^{1}H NMR ($CDCl_3$): δ = 11.9 (br s., 1 H, NH), 8.39 (d, 2 H, J = 8.5 Hz, 2.6 Hz, 6-$H_{imidazol-pyridine}$), 7.59 (m, 3 H, 4-$H_{midazol-pyridine}$ + 2-$H_{arom\text{-}Cl}$ + 6-$H_{arom\text{-}Cl}$), 7.42 (m, 3 H, 3-$H_{arom\text{-}Cl}$ + 5-$H_{arom\text{-}Cl}$ + 5-$H_{imidazol-pyridine}$), 6.97 (dd, 1 H, J = 8.8 Hz, 2.6 Hz, 5-H_{indole}), 6.82 (d, 1 H, J = 8.8 Hz, 4-H_{indole}), 6.59 (d, 1 H, J = 2.6 Hz, 7-H_{indole}), 3.74 (s, 3 H, OMe), 3.64 (s, 2 H, CH_2), 2.30 (s,

3 H, Me). – ^{13}C NMR ($CDCl_3$): δ = 168.3 (C=O), 155.9 (6-C_{indole} + 7a-$C_{imidazol-pyridine}$), 147.0 (2-$C_{imidazol-pyridine}$ + 6-$C_{imidazol-pyridine}$), 139.1 (4-$C_{arom-Cl}$), 135.5 (2-C_{indole} + 7a-C_{indole}), 131.1 (3-$C_{imidazol-pyridine}$), 130.9, 130.7, 127.0, 128.1, 122.0 (C_{arom}), 111.3 (3-C_{indole} + 5-C_{indole}), 101.2 (7-C_{indole}), 55.6 (OMe), 25.2 (CH_2), 13.3 (Me). – $C_{24}H_{19}ClN_4O_2$: calcd. C 66.90, H 4.44, N 13.00; found C 66.78, H 4.38, N 12.79.

*(3-((9H-Purin-8-yl)methyl)-6-methoxy-2-methyl-1H-indol-1-yl)(4-chlorophenyl)methanone (**12**)*

From 4,5-diaminopyrimidine (**6**) (110 mg). Yield: 376 mg (58 %). – ^{1}H NMR ($CDCl_3$): δ = 9.05 (d, 1 H, *J* = 2.2 Hz, 4-H_{purine}), 8.90 (d, 1 H, *J* = 2.2 Hz, 6-H_{purine}), 7.65 (2 H, *J* = 7.0 Hz, 2-$H_{arom-Cl}$ + 6-$H_{arom-Cl}$), 7.46 (d, 2 H, *J* = 7.0 Hz, 3-$H_{arom-Cl}$ + 5-$H_{arom-Cl}$), 6.95 (dd, 1 H, *J* = 8.9 Hz, 2.4 Hz, 5-H_{indole}), 6.84 (d, 1 H, *J* = 8.9 Hz, 4-H_{indole}), 6.67 (d, 1 H, *J* = 2.4 Hz, 7-H_{indole}), 3.81 (s, 3 H, OMe), 3.68 (s, 2 H, CH_2), 2.38 (s, 3 H, Me). – ^{13}C NMR ($CDCl_3$): δ = 168.3 (C=O), 156.0 (6-C_{indole}), 153.1 (7a-C_{purine}); 148.9 (2-C_{purine} + 6-C_{purine}), 139.1 (4-$C_{arom-Cl}$), 136.1 (2-C_{indole} + 7a-C_{indole}), 131.2 (3a-C_{purine} + 4-C_{purine} + 2-$C_{arom-Cl}$ + 6-$C_{arom-Cl}$), 129.1, 128.2, 122.1 (C_{arom}), 120.1 (3a-C_{indole} + 4-C_{indole}), 111.6 (3-C_{indole}), 101.3 (7-C_{indole}), 55.7 (OMe); 23.5 (CH_2); 13.3 (Me). – $C_{23}H_{18}ClN_5O_2$: calcd. C 63.96, H 4.20, N 16.22; found C 63.69, H 4.11, N 16.01.

*(3-(Benzothiazol-2-ylmethyl)-6-methoxy-2-methyl-1H-indol-1-yl)(4-chlorophenyl)methanone (**13**)*

From 2-aminobenzenethiol (**7**) (125 mg). Yield: 368 mg (55 %); oil. – ^{1}H NMR ($CDCl_3$, 600 MHz, HMBC): δ = 8.17 – 7.90 (m, 2 H, 4-$H_{benzothiazole}$ + 7-$H_{benzothiazole}$), 7.66 (d, 2 H, *J* = 8.9 Hz, 2-$H_{arom-Cl}$ + 6-$H_{arom-Cl}$), 7.53 – 7.44 (4 H, 5-$H_{benzothiazole}$ + 6-$H_{benzothiazole}$ + 3-$H_{arom-Cl}$ + 5-$H_{arom-Cl}$), 6.95 (d, 1 H, *J* = 9.0 Hz, 2.4 Hz, 5-H_{indole}), 6.85 (d, 1 H, *J* = 9.0 Hz, 4-H_{indole}), 6.66 (d, 1 H, *J* = 2.4 Hz, 7-H_{indole}), 3.83 (s, 3 H, OMe), 3.70 (s, 2 H, CH_2), 2.38 (s, 3 H, Me). – ^{13}C NMR ($CDCl_3$): δ = 168.3 (C=O), 166.2 (2-$C_{benzothiazole}$), 156.1 (6-C_{indole}), 154.1 (3a-$C_{benzothiazole}$), 139.3 (4-$C_{arom-Cl}$), 136.9 (7a-C_{indole} + 2-C_{indole}), 133.8 (7a-$C_{benzothiazole}$), 131.2, 129.2, 127.6 (1-$C_{arom-Cl}$ + 2-$C_{arom-Cl}$ + 3-$C_{arom-Cl}$ + 5-$C_{arom-Cl}$+ 6-$C_{arom-Cl}$), 125.6 (5-$C_{benzothiazole}$ + 6-$C_{benzothiazole}$), 121.9 (4-$C_{benzothiazole}$ + 7-$C_{benzothiazole}$), 118.9 (4-C_{indole}), 118.3 (3a-C_{indole}), 111.7 (3-C_{indole} + 5-C_{indole}), 101.3 (7-C_{indole}), 55.8 (OMe), 23.5 (CH_2), 13.4 (Me). – HRMS ((+)-ESI): m/z = 446.9590 (calcd. 446.9594 for $C_{25}H_{19}ClN_2O_2S$, $[M]^+$).

*General procedure for the preparation of the imine derivatives of indomethacin **16** – **20***

A solution of **15** (371 mg, 1.0 mmol) in EtOH (15 mL) containing an appropriate ketone (1.1 mmol) was heated under reflux for 3 h. After cooling, the solution was evaporated to dryness, and the residue was partitioned between $CHCl_3$ (2 × 20 mL) and water (20 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the filtrate was evaporated to dryness. The residue was purified by SiO_2 column chromatography using a gradient of MeOH (0 – 10 %) in $CHCl_3$ as eluent to provide the desired product.

*N-(4-tert-Butylcyclohexylidene)-2-(1-(4-chlorobenzoyl)-6-methoxy-2-methyl-1H-indol-3-yl)acetohydrazide (**16**)*

From 4-*tert*-butylcyclohexanone (196 mg). Yield: 416 mg (82 %); m. p. 101 – 105 °C. – ^{1}H NMR ([D_6]DMSO): δ = 10.54 (s, 1 H, NH), 7.64 (dd, 2 H, *J* = 7.7 Hz, 1.8 Hz, 2-$H_{arom-Cl}$ + 6-$H_{arom-Cl}$), 7.48 (dd, 2 H, *J* = 7.7 Hz, 1.8 Hz, 3-$H_{arom-Cl}$ + 5-$H_{arom-Cl}$), 6.98 (d, 1 H, *J* = 2.4 Hz, 7-H_{indole}), 6.88 (d, 1 H, *J* = 8.8 Hz, 4-H_{indole}), 6.69 (dd, 1 H, J = 8.8 Hz, 24 Hz, 5-H_{indole}), 3.81 (s, 3 H, OMe), 3.64 (s, 2 H, CH_2), 2.30 (s, 3 H, Me), 1.37 – 1.02 (m, 18 H, H-^{t}but-cyclohexan). – ^{13}C NMR ([D_6]DMSO): δ = 170.0 (NHN*C*=O), 167.2 (C=O), 156.3 (6-C_{indole} + C=N), 138.1 (4-$C_{arom-Cl}$), 133.9 (7a-C_{indole}), 134.0 (2-C_{indole}), 131.6, 130.2, 129.7 (C_{arom}), 116.8 (3a-C_{indole} + 4-C_{indole}), 110.5 (3-C_{indole}), 109.0 (5-C_{indole}), 100.1 (7-C_{indole}), 55.1 (OMe), 46.9 (4-$C_{cyclohexan}$), 31.8 (CMe_3), 27.1 (2,3,5,6-$C^6_{cyclohexan}$+CMe_3), 13.1 (Me). – $C_{29}H_{34}ClN_3O_3$: calcd. C 68.56, H 6.75, N 8.27; found C 68.36, H 6.68, N 7.93.

*2-(1-Benzoyl-6-methoxy-2-methyl-1H-indol-3-yl)-N′-(1-(5-methylphenyl)-2,2-dimethylpropylidene)acetohydrazide (**17**)*

From 1-(5-methoxy-2-methylphenyl)-2,2-dimethylpropan-1-one (227 mg). Yield: 476 mg (85 %); m. p. 135 – 139 °C. – ^{1}H NMR ([D_6]DMSO): δ = 10.60 (s, 1 H, NH), 7.86 (dd, 2 H, *J* = 6.8 Hz, 1.9 Hz, 2-$H_{arom-Cl}$ + 6-$H_{arom-Cl}$), 7.54 (dd, 2 H, *J* = 6.8 Hz, 1.9 Hz, 3-$H_{arom-Cl}$ + 5-$H_{arom-Cl}$), 7.17 (dd, 1 H, *J* = 8.4 Hz, 1.7 Hz, 4-H_{indole}), 7.08 (d, 1 H, J = 8.8 Hz, 3-H_{arom}), 7.05 (d, 1 H, J = 2.4 Hz, 6-H_{arom}), 6.97 (d, 1 H, *J* = 8.4 Hz, 5-H_{indole}), 6.86 (d, 1 H, J = 1.9 Hz, 7-H_{indole}), 6.63 (dd, 1 H, *J* = 8.6 Hz, 2.4 Hz, 4-H_{arom}), 3.75, 3.73 (2xs, 6 H, 2xOMe), 3.36 (s, 2 H, CH_2); 2.34 (s, 3 H, Me), 1.32 (s, 6 H, CMe_3). – ^{13}C NMR ([D_6]DMSO): δ = 170.2 (NHN*C*=O), 164.8 (C=O), 153.0 (6-C_{indole} + 5-C_{arom}), 152.8 (C=N), 135.9 (4-$C_{arom-Cl}$), 133.7 (7a-C_{indole}), 132.0 (2-C_{indole}), 130.4, 130.1, 129.0, 128.8, 128.3, 126.3 (C_{arom}), 111.3 (3a-C_{indole} + 4-C_{indole}), 110.7 (5-C_{indole} + 6-C_{arom}), 109.3 (4-C_{arom}), 104.6 (3-C_{indole}), 100.7 (7-C_{indole}), 55.4 (2xOMe), 29.7 (CH_2C=O), 26.5 (CMe_3), 19.9, 11.6 (2xMe). – $C_{32}H_{34}ClN_3O4_5$: calcd. C 68.62, H 6.12, N 7.50; found C 68.41, H 6.01, N 7.21.

*2-(1-(4-Chlorobenzoyl)-6-methoxy-2-methyl-1H-indol-3-yl)-N-((4-methoxyphenyl)(phenyl)methylene)acetohydrazide (**18**)*

From (4-methoxyphenyl)(phenyl)methanone (233 mg). Yield: 447 mg (79 %); m. p. 142 – 145 °C. – ^{1}H NMR ([D$_6$]DMSO): δ = 9.08 (s, 1 H, NH), 7.86 – 6.62 (m, 16 H, H$_{arom}$), 3.75 (2xs, 6 H, 2xOMe), 3.37 (s, 2 H, CH$_2$); 2.34 (s, 3 H, Me). – ^{13}C NMR ([D$_6$]DMSO): δ = 170.7 (NHN*C*=O), 165.3 (C=O), 153.4 (6-C$_{indole}$ + C=N + C$_{arom}$-OMe), 137.8 (4-C$_{arom-Cl}$), 136.8 (7a-C$_{indole}$), 134.2 (2-C$_{indole}$), 132.9, 132.5, 130.6, 130.3, 129.9, 129.3, 128.9 (C$_{arom}$), 111.8 (4-C$_{indole}$ + C$_{arom}$ + 3a-C$_{indole}$), 109.8 (5-C$_{indole}$), 105.8 (3-C$_{indole}$), 101.1 (7-C$_{indole}$), 55.9 (2 × OMe), 30.2 (*C*H$_2$C=O), 12.1 (Me). – $C_{33}H_{28}ClN_3O_4$: calcd. C 70.02, H 4.99, N 7.42; found C 69.78, H 4.92, N 7.21.

*N-(2-Amino-2-methyl-1-phenylpropylidene)-2-(1-(4-chlorobenzoyl)-6-methoxy-2-methyl-1H-indol-3-yl)-N-((4-methoxyphenyl)(phenyl)methylene)acetohydrazide (**19**)*

From 2-amino-2-methyl-1-phenylpropan-1-one (179 mg). Yield: 403 mg (78 %). – ^{1}H NMR ([D$_6$]DMSO): δ = 10.79 (s, 1 H, NH), 8.69 (m, 2 H, NH$_2$), 7.59 – 6.62 (m, 12 H, H$_{arom}$), 3.72 (s, 3 H, OMe), 3.45 (s, 2 H, CH$_2$), 2.29 (s, 3 H, Me), 1.07, 1.03 (m, 6 H, 2xCMe$_2$). – ^{13}C NMR ([D$_6$]DMSO): δ = 173.1 (NHNH*C*=O), 166.9 (C=O), 155.9 (6-C$_{indole}$ + C=N, 136.4 (4-C$_{arom-Cl}$ + 7a-C$_{indole}$ + 2-C$_{indole}$), 130.2, 129.9, 129.7, 128.9, 128.8, 128.2 (C$_{arom}$), 111.2 (4-C$_{indole}$ + C$_{arom}$ + 3a-C$_{indole}$), 109.8 (5-C$_{indole}$), 102.2 (3-C$_{indole}$), 99.6 (7-C$_{indole}$), 56.0 (*C*Me$_3$), 55.4 (OMe), 30.0 (CH$_2$C=O), 24.4, 23.7 (C*Me*$_2$), 12.2 (Me). – $C_{29}H_{29}ClN_4O_3$: calcd. C 67.37, H 6.86, N 10.84; found C 67.06, H 5.48, N 10.57.

*2-(1-(4-Chlorobenzoyl)-6-methoxy-2-methyl-1H-indol-3-yl)-N-(1,2-diphenylethylidene)acetohydrazide (**20**)*

From 1,2-diphenylethanone (215 mg). Yield: 467 mg (85 %). – ^{1}H NMR ([D$_6$]DMSO): δ = 10.50 (s, 1 H, NH), 7.86 – 6.98 (m, 17 H, H$_{arom}$), 3.69 (s, 3 H, OMe), 3.44 (s, 2 H, CH$_2$), 2.34 (s, 3 H, Me). – ^{13}C NMR ([D$_6$]DMSO): δ = 174.0 (NHN*C*=O), 167.9 (C=O), 160.6 (6-C$_{indole}$), 152.9 C=N), 141.8 (4-C$_{arom-Cl}$ + 1-C$_{benzyl}$), 137.5 (7a-C$_{indole}$), 136.3 (2-C$_{indole}$), 129.6, 128.7, 128.5, 128.3, 128.1, 128.0, 126.4 (C$_{arom}$), 110.8 (4-C$_{indole}$ + 3a-C$_{indole}$), 109.6 (5-C$_{indole}$), 104.4 (3-C$_{indole}$), 100.0 (7-C$_{indole}$), 54.8 (OMe), 31.5 (*C*H$_2$C=O), 28.3 (*C*H$_2$Ph), 11.7 (Me). – $C_{33}H_{28}ClN_3O_3$: calcd. C 72.06, H 5.13, N 7.64; found C 71.89, H 5.04, N 7.51.

*2-(1-(4-Chlorobenzoyl)-6-methoxy-2-methyl-1H-indol-3-yl)-N-(phenylcarbonothioyl)acetohydrazide (**21**)*

A suspension of **15** (371 mg, 1.0 mmol) and phenyl isothiocyanate (135 mg, 1.0 mmol) in EtOH (10 mL) was heated under reflux for 6 h. The solvent was evaporated to dryness, and the residue was worked up as in **20** to give **21** (297 mg, 78 %). – ^{1}H NMR ([D$_6$]DMSO): δ = 10.02, 9.60 (2d, 2 H, *J* = 4.8 Hz, NH), 7.99 – 6.61 (m, 12 H, H$_{arom}$), 3.34 (s, 3 H, OMe), 3.54 (s, 2 H, CH$_2$), 2.31 (s, 3 H, Me). – ^{13}C NMR ([D$_6$]DMSO): δ = 187.3 (C=S=S), 171.7 (NHN*C*=O), 168.7, 165.0 (C=O), 139.1, 134.0, 131.3, 130.1, 129.7, 128.7, 128.3, 128.0 (C$_{arom}$), 124.9 (3a-C$_{indole}$ + 4-C$_{indole}$), 110.8 (3-C$_{indole}$), 103.9 (5-C$_{indole}$), 100.4 (5-C$_{indole}$), 55.3 (OMe), 29.7 (CH$_2$), 11.6 (Me). – $C_{26}H_{22}ClN_3O_3S$: calcd. C 63.47, H 4.51, N 8.54; found C 63.21, H 4.47, N 8.17.

*(3-(1,3,4-Oxadiazol-2-yl)methyl-6-methoxy-2-methyl-1H-indol-1-yl)(4-chlorophenyl)methanone (**22**)*

A mixture of **15** (371 mg, 1.0 mmol) and triethyl orthoformate (5 mL) was heated under reflux for 12 h. After cooling, the solvent was evaporated, and the residue was purified on a short SiO_2 column. Elution, in gradient, with MeOH (0 – 10 %) and $CHCl_3$ as eluent provided **22** (305 mg, 62 %). – ^{1}H NMR ([D$_6$]DMSO): δ = 9.34 (s, 1 H, 5-H$_{oxadiazole}$), 8.03 – 6.63 (m, 7 H, H$_{arom}$), 3.75 (s, 3 H, OMe), 3.67 (s, 2 H, CH$_2$), 2.21 (s, 3 H, Me). – ^{13}C NMR ([D$_6$]DMSO): δ = 169.1 (C=O), 165.5 (2-C$_{oxadiazol}$), 162.7 (6-C$_{indole}$), 153.3 (5-C$_{oxadiazol}$), 136.6, 133.8, 130.0, 129.4, 129.2, 128.3, 128.0 (C$_{arom}$), 121.9 (3a-C$_{indole}$ + 4-C$_{indole}$), 110.6 (3-C$_{indole}$), 109.4 (5-C$_{indole}$); 102.6 (C^5$_{indole}$), 55.1 (OMe), 19.8 (CH$_2$), 11.5 (Me). – $C_{20}H_{16}ClN_3O_3$: calcd. C 62.91, H 4.22, N 11.01; found C 62.69, H 4.16, N 10.76.

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