Design and synthesis of Mannich base-type derivatives containing imidazole and benzimidazole as lead compounds for drug discovery in Chagas Disease

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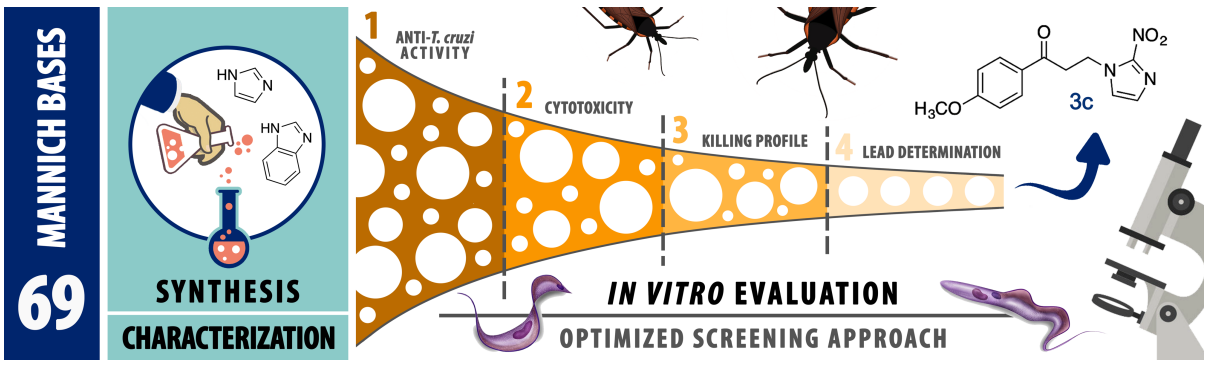
GRAPHICAL ABSTRACT



ABSTRACT

The protozoan parasite *Trypanosoma cruzi* is the causative agent of Chagas Disease, the most important parasitic infection in Latin America. The only treatments currently available are nitro-derivative drugs that are characterised by high toxicity and limited efficacy. Therefore, there is an urgent need for more effective, less toxic therapeutic agents. We have previously identified the potential for Mannich base derivatives as novel inhibitors of this parasite. To further explore this family of compounds, we synthesized a panel of 69 new analogues, based on multi-parametric structure-activity relationships, which allowed optimization of both anti-parasitic activity, physicochemical parameters and ADME properties. Additionally, we optimized our *in vitro* screening approaches against all three developmental forms of the parasite, allowing us to discard the least effective and trypanostatic derivatives at an early stage. We ultimately identified derivative **3c**, which demonstrated excellent trypanocidal properties; both its druggability and low-cost production make this compound a promising candidate for the preclinical, *in vivo* assays of the Chagas disease drug-discovery pipeline.

KEYWORDS: Mannich bases, imidazole, benzimidazole, Chagas disease, neglected tropical diseases, *Trypanosoma cruzi*.

HIGHLIGHTS:

- Imidazole and benzimidazole Mannich bases as new candidates against Chagas disease.
- Efficient screening strategy for the evaluation of new 69 Mannich bases against *T. cruzi*.
- A 2'-nitroimidazole derivative identified as candidate to block the infection *in vitro*.
- The 2'-nitroimidazole **3c** synergizes with benznidazole in combinatory therapy *in vitro*.

1. Introduction

Chagas disease (CD) is the main parasitic infection in Latin America. It is caused by the protozoan *Trypanosoma cruzi*, which is transmitted to humans by triatomine insect vectors. [1]. About 6-8 million people are currently infected and more than 70 million people are at risk of acquiring the disease. Unfortunately, less than 1% of people infected with *T. cruzi* have access to diagnosis and treatment [2]. Other modes of transmission (congenital, blood transfusions, organ transplants, and ingesting contaminated food or drink), as well as global migratory movements, have spread CD to previously unaffected regions and continents. To date, there are only two available treatments, benznidazole (BZ) and nifurtimox (NFX). Both are close to 100% effective if given soon after infection, but they are not approved for use against the symptomatic chronic form of the disease. Additionally, both drugs have drawbacks, with long treatment periods (60-90 days) and dose-dependent toxicity leading to high drop-out rates amongst patients [2-4]. Novel alternative approaches proposed and developed by groups such as the Drugs for Neglected Diseases *initiative* (DND*i*), include new candidate compounds and modifications of existing drug regimens (lower doses, shorter treatment durations and combinations). A new BZ monotherapy regimen, BZ/fosravuconazole combination therapy, and clinical trials of fexinidazole are examples of this [2]. However, despite these efforts, more effective new drugs that are cheaper, safer and more effective than BZ and NFX, have yet to be found [5].

Many compounds have been shown to have biological activity against *T. cruzi,* as demonstrated in our previous research [6]. Of note are the arylamine Mannich base-type derivatives, a family of compounds with the ability to inhibit the iron-containing superoxide dismutase (Fe-SOD). The trypanosomatid isoform of this metalloenzyme, which uses iron as cofactor, is not commonly found in eukaryotes [6]. In addition, this group of compounds display other interesting biological activities, including analgesic, anti-bacterial, anti-cancer, anti-convulsant, anti-fungal, anti-inflammatory, antioxidant and anti-viral properties, among others [7,8]. Thus, Mannich bases represent promising alternatives to current anti-parasitic agents, due to their potential biological activity against parasites responsible for tropical diseases such as trypanosomiasis [9], leishmaniasis [10-12] and malaria [13-16]. Our group has continued this line of research via the incorporation of an array of amine fragments and substituents into the general structure of the Mannich bases [17-20], in an attempt to enhance their anti-chagasic and general anti-parasitic activity.

The discovery pipeline for the development of pre-clinical drug candidates can be a lengthy process, with an urgent need to design new, more rapid and efficient methodologies. High-throughput screening (HTS) approaches are being increasingly used in drug discovery against

parasitic diseases, such as CD, due to the rapidity of the process, the highly informative data generated, and the excellent reproducibility [21-24]. However, although HTS allows many compounds to be tested simultaneously, they produce a high number of 'false-positive' hits. This is mainly due to the lack of detailed assays to properly assess the activity profile of these compounds, for example, discriminating between trypanocidal and trypanostatic properties. Therefore, we have developed an optimized strategy for testing small to medium series of compounds (<100) that allows those with low activity to be discarded early in the discovery cascade, the selection of pre-candidates with confirmed trypanocidal activity, and the synthesis of chemically related compounds using the pre-candidate(s) as scaffolds. This approach introduces a significant reduction in the number of assays, time, materials and costs. The selection process ensures that only promising compounds *in vitro* can be progressed to *in vivo* assays. As the strategy progresses, the assays become more physiologically relevant, providing valuable information on the kinetics of the killing profile of each candidate.

Heterocyclic compounds are a widely studied group that have gained relevance in recent years in medicinal chemistry research. Imidazole and benzimidazole rings, in particular, have occupied a notable position in nitrogen-containing heterocyclic chemistry. Benzimidazole is formed by the fusion of imidazole, a five-membered aromatic framework containing two nitrogen atoms, and benzene. Both heterocycles display amphoteric and highly polar properties. Moreover, they can easily form diverse, weak binding interactions with a variety of proteins, enzymes and receptors in biological systems, displaying broad pharmacological properties and applications. These pharmacophores have gained significant importance and have been used for many years to treat parasitic diseases including CD, with several imidazole and benzimidazole derivatives having potent anti-*T. cruzi* activity [25]. We have therefore further explored the potential of these two heterocyclic moieties in the design and development of new candidates against *T. cruzi*. A total of 69 Mannich base-type derivatives containing imidazole and benzimidazole components are presented in this paper as novel candidates against *T. cruzi*. Our work also introduces a new *in vitro* screening strategy, which has allowed rapid and efficient evaluation of this small library of compounds.

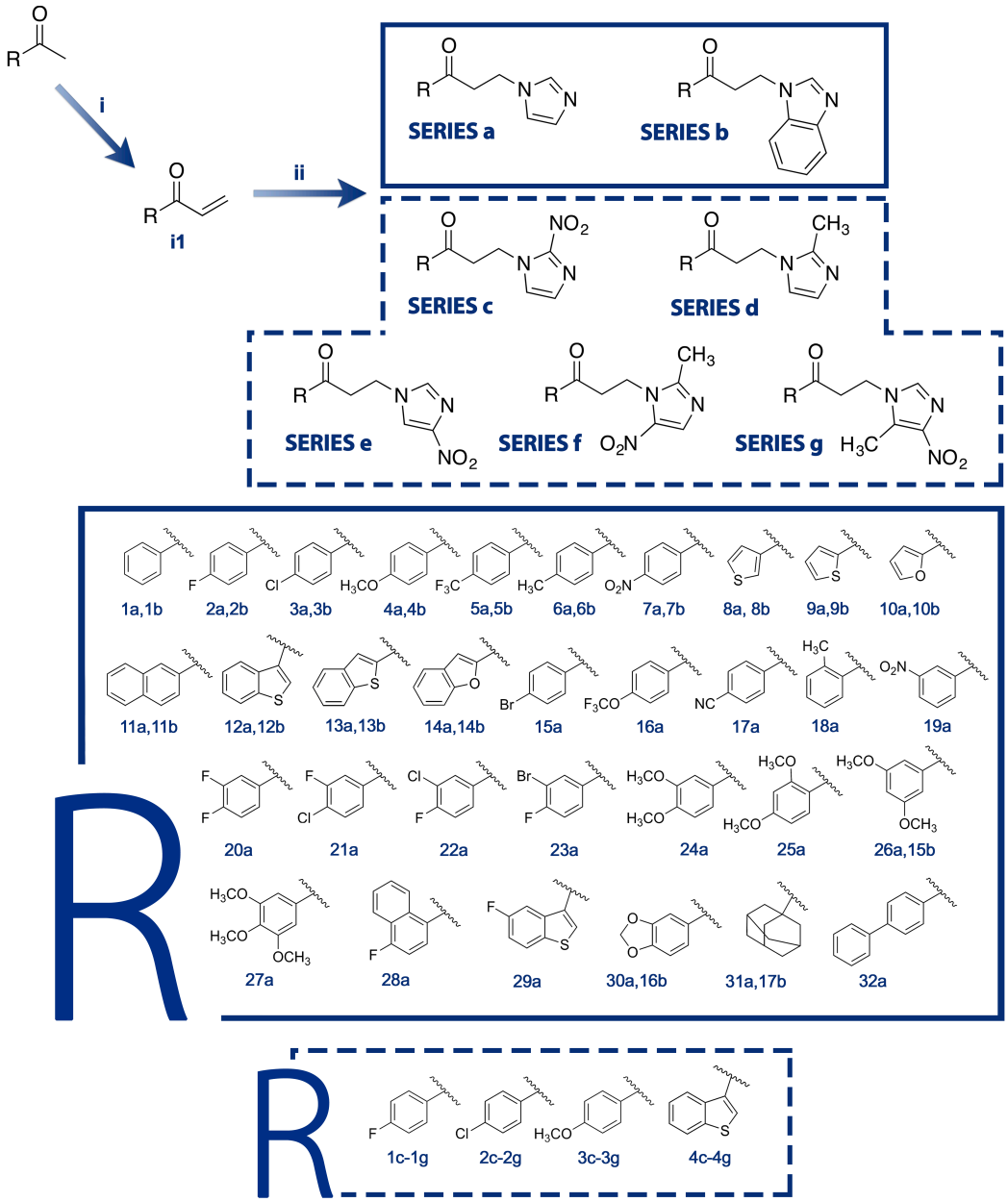
2. Results and discussion

2.1 Chemistry

Based on our group's previous experience in the synthesis of trypanocidal compounds [17-20], we focused our attention on Mannich base derivatives as their synthesis pathways are simple, cost-effective and make use of commercially available chemical reagents. The precise route of synthesis chosen is outlined in **Scheme 1**, in which the vinyl ketone (**i1**) was obtained from the

corresponding methyl ketone (commercially available) using a diisopropylammonium 2,2,2-trifluoroacetate catalyst and paraformaldehyde, in tetrahydrofuran (THF), under reflux and acidic conditions [26]. The following step describes the condensation of the imidazole/benzimidazole ring (**ii**) with the previously synthesised vinyl ketone, via a Michael addition reaction at room temperature.

IR, ^{1}H NMR and ^{13}C NMR spectroscopic data, elemental microanalysis (C, H, N) and electrospray ionisation mass spectra (MS-LC TOF), were required for the full characterisation of all of these new derivatives, as detailed in the **Experimental section**. In some cases, for an accurate assignment of the signals in the ^{1}H and ^{13}C NMR spectra, which were registered in deuterated dimethylsulfoxide (DMSO-d_6), DEPT-135 and heteronuclear simple quantum coherence (gHSQC) experiments were performed.



Scheme 1. Reagents and conditions for the synthesis of 69 Mannich base derivatives: (**i**) paraformaldehyde, diisopropylammonium 2,2,2-trifluoroacetate, trifluoroacetic acid, THF, reflux, 8 h; (**ii**) THF, K_2CO_3, rt, from 24 to 72 h.

2.2 Killing profile of the lead compounds: IC_{50}, SI determination and kinetics of epimastigote killing

Preliminary screening allowed us to select 8 lead compounds (**7a**, **18a**, **19a**, **21a**, **28a**, **15b**, **17b** and **3c**) (see **Supplementary section**), which showed activity against *T. cruzi* CL-Luc:Neon clone epimastigotes [27] and limited toxicity to BSR mammalian cells, from an initial library of 69 nitroheterocyclic derivatives. Their IC_{50} and SI values against epimastigotes and BSR cells were then determined (**Table 1**) according to the methodology described in the **Experimental**

section. Compound **3c** was the most promising candidate, with a lower IC_{50} value than BZ. We also followed the growth rate of drug-exposed parasites in real time by monitoring fluorescence for 7 days (**Experimental section**). Reference drug BZ is considered "fast-killing", as a single dose can decrease the parasitaemia drastically in 24 h in animal models [28]. Consistent with this, at all effective BZ concentrations (>2.5 μM), parasite growth had dropped by day 3 of the treatment (**Figure 1A**). A similar profile was shown by derivative **3c** (**Figure 1B**).

Table 1. IC_{50} values (μM) for inhibition of the growth of *T. cruzi* CL-Luc:Neon clone epimastigotes and for the cytotoxicity toward BSR host cells of selected compounds. **BZ** has been included as a reference drug. Data are presented as the mean ± SD of triplicates of three independent experiments after 72 h exposure. Yellow shading highlights compounds selected for further evaluation.

Compound	IC_{50} (mean ± SD), μM		Selectivity Index (SI)
	Epimastigotes	BSR Cells	
7a	**12.9 ± 1.8**	**93.9 ± 1.9**	**7**
18a	21.4 ± 1.2	144.6 ± 5.8	7
19a	**21.6 ± 4.0**	**177.4 ± 1.8**	**8**
21a	23.3 ± 4.9	134.6 ± 2.7	6
28a	**7.4 ± 0.5**	**72.2 ± 1.2**	**10**
15b	11.1 ± 3.2	70.1 ± 9.6	6
17b	24.8 ± 5.8	67.6 ± 6.1	3
3c	**2.2 ± 0.6**	**84.7 ± 1.2**	**43**
BZ	3.8 ± 0.7	267.3 ± 1.3	67

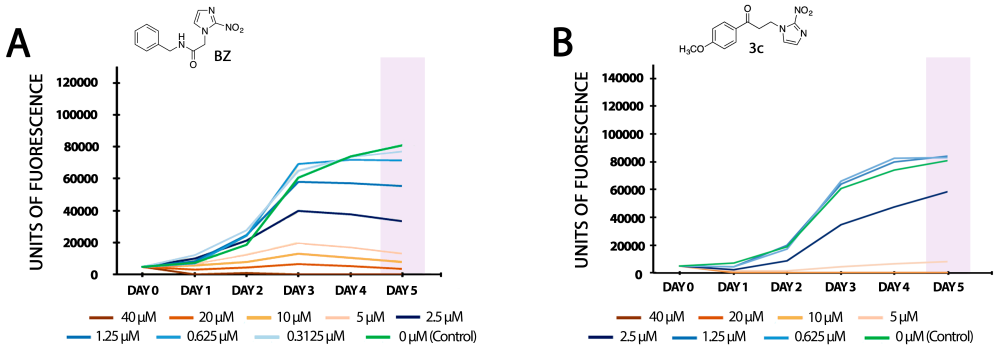


Figure 1. Kinetics of growth inhibition of *T. cruzi* CL-Luc:Neon clone epimastigotes over time in the presence of **BZ** (**A**) and compound **3c** (**B**). Data are presented as units of fluorescence, obtained by real time fluorescence readout for 5 days, by which time epimastigotes had reached the stationary phase.

2.3 Drug-like Properties

Employing the Molinspiration [29] and Osiris Data Warrior [30] software, compounds (**7a**, **19a, 28a** and **3c**) were analysed to predict their physiochemical properties, in relation to absorption

and bioavailability (**Table 2)**. None of the derivatives, including BZ, violated the Lipinski's rule of five [31]. It has been well established that optimal lipophilicity range, along with low logP (<5) and low topological polar surface area (TPSA), are the major driving forces that lead to good absorption, including intestinal absorption, bioavailability, Caco-2 cell permeability, and blood-brain barrier penetration. Molecules with a TPSA of <140 $Å^2$ are indicative of excellent bioavailability [32]. The calculated logP and TPSA values for derivatives **7a**, **19a, 28a** and **3c** range from 0.12 to 2.51, suggesting that these compounds should be able to cross cell membranes. This was confirmed by their ability to kill epimastigotes.

The drug score combines drug likeness, logP, molecular weight and toxicity risks in one handy value that can be used to infer therapeutic potential. A value of >0.5 indicative of theoretical promise as a safe and efficient drug [33]. Compounds **3c** had the highest drug score (0.61) among the evaluated compounds. For comparison, the BZ displays a drug score of 0.33.

Table 2. Theoretical molecular properties for selected compounds **7a**, **19a, 28a** and **3c**.

Molecular Properties (Molinspiration and Osiris Calculations)

Compound	MW	cLogP	cLogS	TPSA	H Acep	H Donor	NV	Vol	Drug LK	Drug Score
7a	245.24	0.12	-2.15	80.72	6	0	0	212.58	-1.35	0.57
19a	245.24	0.12	-2.15	80.72	6	0	0	212.58	-1.35	0.57
28a	268.29	2.51	-3.61	34.89	3	0	0	238.17	2.43	0.43
3c	275.26	0.42	-2.43	89.95	7	0	0	238.13	-2.55	0.61
BZ	260.25	0,12	-2.15	92.75	7	1	0	224.99	-1.71	0.33

2.4 IC_{50} and SI determination against amastigotes and trypomastigotes.

We also evaluated the ability of compounds **7a**, **19a**, **28a** and **3c** to inhibit the replication of intracellular amastigotes (**Table 3**). Amastigotes are the most clinically relevant life-cycle stage in the mammalian host. Effective drugs must be able to cross the host cell membrane to act against the parasite. The IC_{50} values, which were calculated after 3 days exposure (see **Experimental section**), revealed that derivatives **28a** and **3c** were similarly effective against both epimastigotes and amastigotes. In contrast, compounds **7a** and **19a** were more effective against amastigotes, although the IC_{50} values were still relatively modest, at 9.1 and 12.2 μM, respectively.

Non-replicative trypomastigotes are the parasite forms responsible for cellular invasion, as well as the form taken up by the insect vectors in a blood meal from an infected host. We tested the selected compounds against this flagellated extracellular form (**Experimental section).** Compounds **28a** and **3c** were the most active derivatives, with IC_{50} values of 16.6 and 9.1 μM,

respectively, even more active than BZ (22.4 μM). Compound **19a** displayed similar activity to the reference drug. In contrast, derivative **7a** was inactive against this parasitic form and discarded from future assays.

Table 3. IC_{50} values (μM) against *T. cruzi* amastigotes and trypomastigotes of compounds **7a**, **19a**, **28a** and **3c**. **BZ** was included as a reference drug. Data are presented as the mean ± SD of triplicates of three independent experiments after 72 h of incubation. nd, non-determined.

Compound	IC_{50} (mean ± SD), μM			Selectivity Index (SI)	
	Amastigotes	Trypomastigotes	BSR Cells	Amastigotes	Trypomastigotes
7a	9.1 ± 0.6	nd	93.9 ± 1.9	10	nd
19a	12.2 ± 1.7	23.0 ± 1.0	177.4 ± 1.8	15	8
28a	6.1 ± 1.6	16.6 ± 0.3	72.2 ± 1.2	12	4
3c	3.3 ± 1.3	9.1 ± 2.3	84.7 ± 1.2	28	9
BZ	0.5 ± 0.1	22.4 ± 3.5	267.3 ± 1.3	504	12

2.5 Wash-out Assays

To fully understand the activity profile of compounds **19a**, **28a** and **3c,** we undertook wash-out assays, modifying a protocol described by Cal *et al*. [34] (**Experimental section**). The usefulness of this assay has become more apparent since the advent of high-throughput screening technologies. It allows viable persistent parasites that survive treatment, because of their reduced drug susceptibility, to be identified [35]. This assay provides an early insight into the potential for compound failure, before their use in animal models. In the wash-out assay, parasite-infected cells were exposed to high test compound concentrations (10 and 20 x IC_{50}) for either 10 or 20 days, after which the compound was removed from the culture medium. Infected and treated cultures were then monitored by fluorescent microscopy for a further 30 days after removal of the drugs, to investigate parasite relapse (**Figure 2**). By day 3 post-treatment, there was growth inhibition (**Figure 2A).** However, in all cases where less than 10 x IC_{50} treatment conditions were used, renewed parasite growth was detectable, regardless of whether initial exposure was for 10 or 20 days. In the case of derivatives **19a** and **28a**, where due to host cell toxicity, we could only use the 10 x IC_{50} concentration, intact parasites could still be seen after 10 days treatment (**Figure 2B-D**). Even with 20 days exposure, dividing parasites were detectable 10 days after compound removal (**Figure 2H**), indicative of a trypanostatic mode of action for these derivatives. By contrast, both the reference drug BZ and compound **3c** could be inferred to have a strong trypanocidal effect when given for 20 days at the 20 x IC_{50} concentration. By day 10 post-exposure, this type of trypanocidal profile was already visible,

with apparently destroyed parasites, some of which were broken up, and others already taken into the lysosomal pathway of host cells for degradation (**Figure 2F**). Even 30 days after drug removal (**Figure 2I**), the BZ and compound **3c** cultures remained clear of parasites. Collectively, these results confirm that **3c** can eliminate *T. cruzi* intracellular stages, without the survival of persistent parasites.

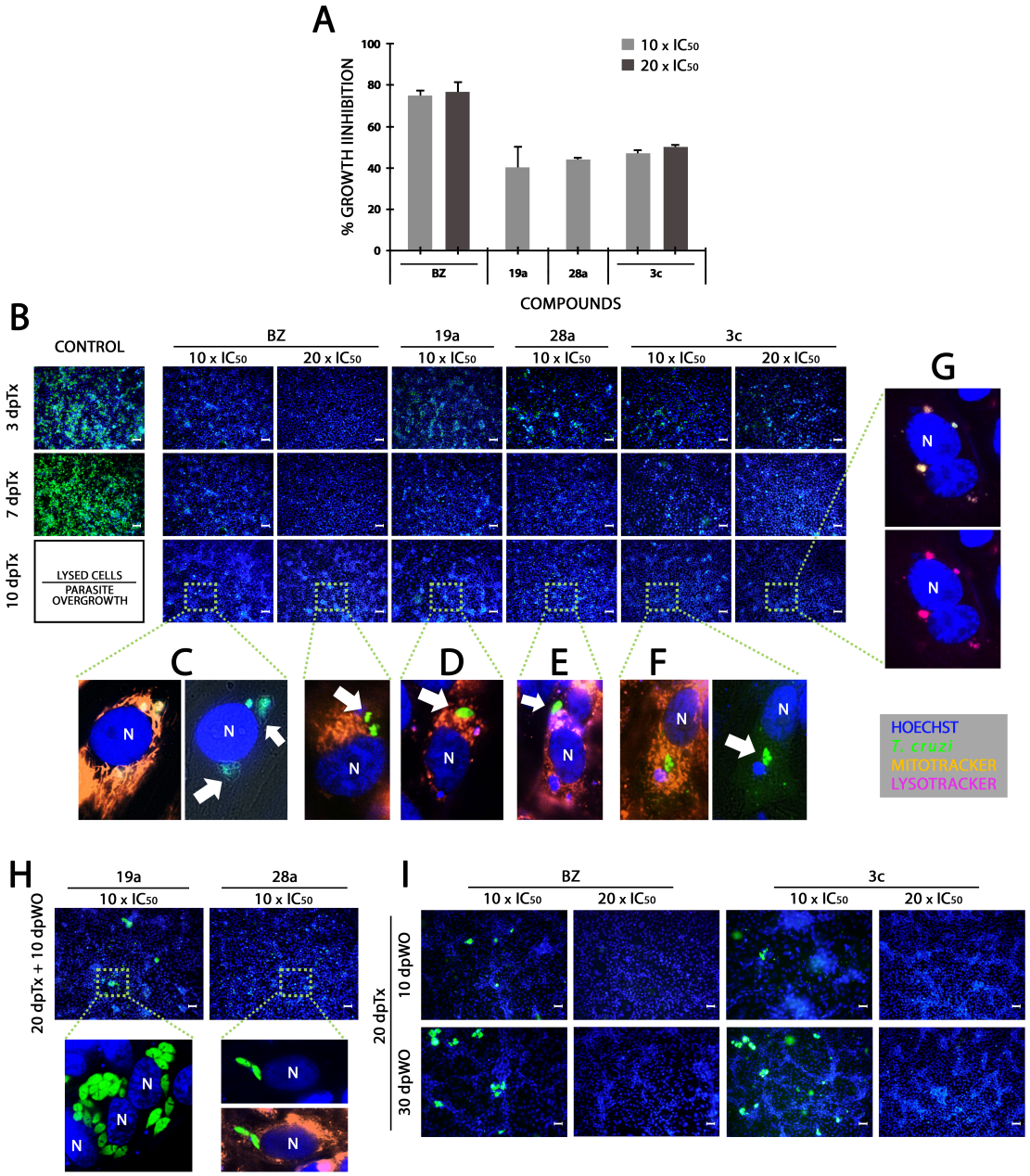


Figure 2. Wash-out assays for **BZ** and derivatives **19a**, **28a** and **3c** against *T. cruzi* CL-Luc:Neon clone amastigotes in BSR infected cells. **A**, Growth inhibition after 72 h treatment measured as fluorescent intensity compared to untreated group. **B**, Representative fields (of 30 captures per treatment) from the treated wells under epifluorescence microscopy at different timepoints post-treatment. **C**, **D**, **E**, **F**, **G**, **H** and **I**. Representative zoomed areas of interest under different treatments visualised by epifluorescence microscopy. Cell dyes (mitotracker and lysotracker) are used for a better location of parasites in the intracellular domain. dpTx, days post-treatment; dpWO, days post drug wash-out. N, mammalian cell nuclei. White arrows indicate parasites. Scale bars = 50 μm.

2.6 Infectivity assay

Trypomastigotes are often more refractory to drug treatment than the replicating amastigote form, which is consistent with the obtained IC_{50} values (**Table 3**). For these assays, we determined the drug concentrations that reduced trypomastigote infectivity by 50% compared to untreated control. We also sought to determine the minimal concentration of drug required to produce a sterile infection following 6 h incubation with trypomastigotes. Using fluorescence microscopy, we found that pre-exposure to **3c** at concentrations >50 μM completely blocked trypomastigote infectivity. In contrast, even at BZ concentrations >100 μM, some persistent parasites were observed 5 days post-infection (**Figure 4**). Whether the impact of **3c** on infection was due to trypomastigotes being killed directly by drug action, or by damage that prevents them infecting host cells remains unknown.

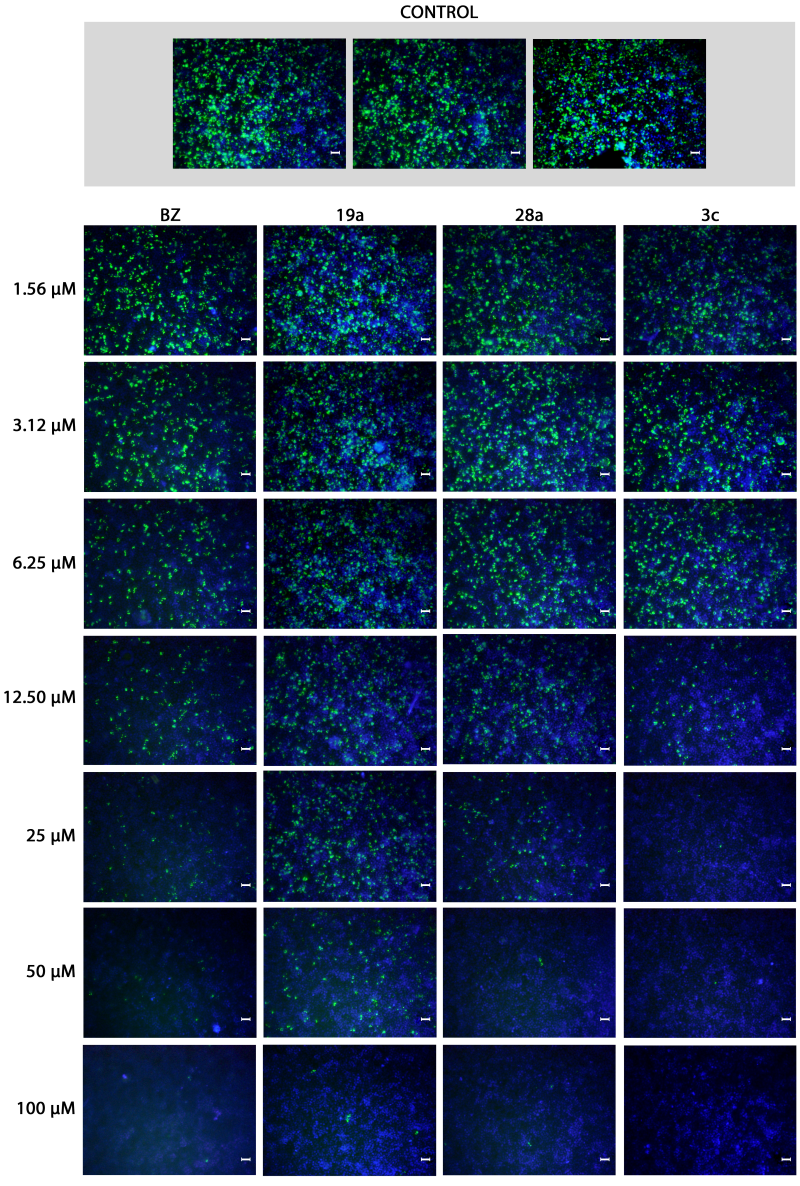


Figure 4. Infectivity assays of *T. cruzi* CL-Luc:Neon trypomastigotes pre-treated with **BZ** or derivatives **19a**, **28a** and **3c** for 6 h prior to infection of BSR cells (Experimental section). Values were established from amastigote fluorescence 5 days post-infection. Images of broad field captures are shown at 20x under epifluorescence microscopy for increasing drug concentrations. These are representative of 30 images taken per treatment. Host-cell nuclei are shown in blue (DAPI staining), with parasites in green; scale bars = 50 μm.

2.7 *In vitro* toxicity screening: Comet Assay

The formamide pyrimidine DNA glycosylase (Fpg)-modified comet assay was performed to check the potential genotoxic effect of derivative **3c** on human cells. To do so, we used the human lymphoblastoid TK-6 cell line, which is widely used in genotoxicity testing since they are p53-competent (recommended by several OECD guidelines for *in vitro* genotoxicity and mutagenicity assays).

This version of the assay detects both DNA strand breaks (SBs) and oxidised/alkylated bases [36,37]. To prevent a misinterpretation of the comet assay readout due to widespread DNA degradation induced by lethal doses, we simultaneously ran a proliferation assay. The latter acts to confirm cell integrity. DNA damage associated with cells under conditions where proliferation is inhibited by >25 % is considered a false positive outcome with the comet assay. **Figure 5** shows the results obtained in the Fpg-modified and the proliferation assays after 3 h of treatment. A 46% decrease in proliferation was observed in TK-6 cells treated with 40 μM **3c** (data not shown), and for the reasons explained, comet assays were not performed at concentrations up to and beyond this limit. For all the concentrations below, the levels of SBs and Fpg-sensitive sites were not significantly different ($p>0.05$) from the untreated controls. In contrast, analysis of cells treated with 20 μM of the DNA alkylating agent MMS (methyl methanesulphonate), which were included a positive control, revealed extensive genotoxic damage (**Figure 5**). Collectively, these results are consistent with a safe profile for compound **3c**, in terms of DNA damage, over the concentration range at which it is therapeutically active against the different forms of *T. cruzi*.

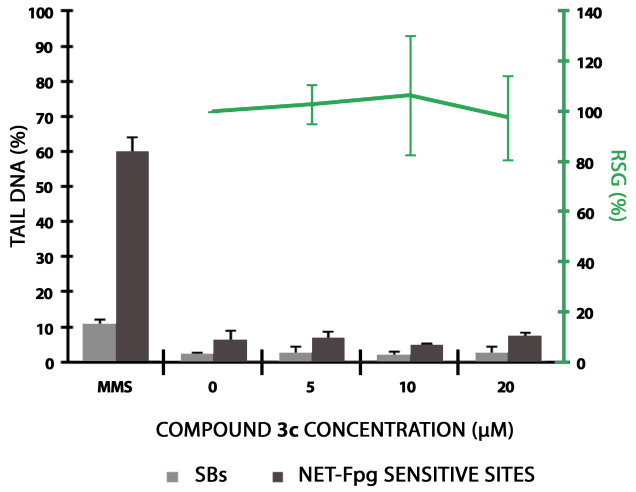
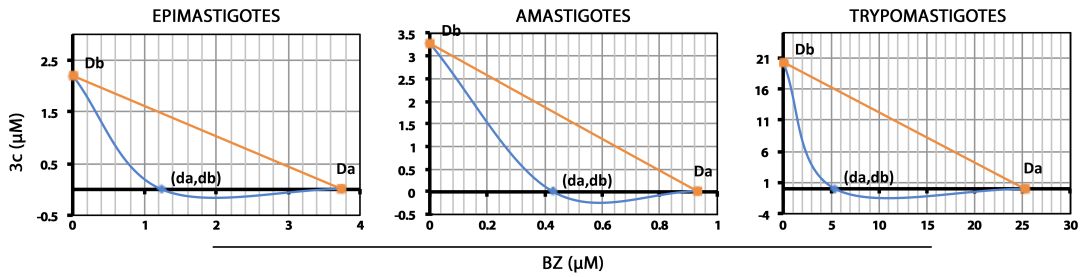


Figure 5. Comet and proliferation assays performed on **3c**-treated TK-6 cells after 3 h exposure. SBs and Net-Fpg sensitive sites are represented as a percentage of the DNA in the comet's tail relative to the DNA remaining in the comet. SBs and Fpg-sensitive sites were not statistically different under all conditions tested when compared to control valves ($p>0.05$). For the proliferation assay, cells were washed after the treatment and cultured for 48 h. Cells were then counted and the relative suspension growth (RSG) was calculated (Experimental section) in relation to the untreated control. Results are presented as the mean ± SD of triplicates of three independent experiments. MMS-treated cells (20 μM) were included as a positive control for DNA damage.

2.7 Drug combination assay

Whilst BZ is effective in long regimens, toxicity is a major reason for low rates of compliance, which ultimately leads to treatment failure. There is a strong rationale to search for compounds that in combination with BZ can allow its dosage and/or treatment period to be reduced, while obtaining similar curative rates. The trypanocidal effect of derivative **3c** against trypomastigotes, with activity greater than BZ, encouraged us to undertake a combinatory assay. The results (**Figure 6**) showed a synergic effect of **3c** on the BZ IC_{50}. While this effect was minimal against intracellular forms, it was prominent against both extracellular forms. In the case of the epimastigotes (insect vector forms), **3c** decreased the BZ IC_{50} by almost 70%, in comparison with a single treatment of BZ. The synergic effect was even greater in the case of trypomastigotes (mammalian infective forms), where the IC_{50} value dropped to almost a quarter of that obtained for BZ alone.

A



B

T. cruzi Form	IC_{50} (mean ± SD), μM		Ci	BZ IC_{50} Fold Decreased in Combination
	BZ	BZ + 3c		
Epimastigote	3.8 ± 0.7	1.2 ± 0.1	0.33	3x
Amastigote	0.5 ± 0.1	0.4 ± 0.1	0.81	-
Trypomastigote	22.4 ± 3.5	5.4 ± 1.7	0.21	4x

Figure 6. Drug combination assay. A, isobolograms of concentration-effect curves of **3c** and **BZ** and their combinations against different developmental forms of *T. cruzi*. B, table showing the variation of BZ IC_{50} when the assays were performed in the presence of the IC_{50} concentrations of **3c**; Ci (coefficient of interaction) shows the synergic relation between drugs (Ci < 1). Data are shown as mean ± SD (n = 3). Orange lines link the IC_{50} values for drugs assayed independently (Da, **BZ**; Db, **3c**), while blue lines show the shift of the IC_{50} for **BZ** (da) assayed in the presence of **3c** (db).

3. CONCLUSION

In summary, we synthesised and characterised a total of 69 Mannich base-type derivatives bearing imidazole and benzimidazole-functionalized cores. *In vitro* cell-based studies demonstrated that, of these, compound **3c** had the most promising trypanocidal activity across the distinct life stages of the parasite. It displayed fast-killing activity at low micromolar doses, lacked host cell genotoxicity, and had a synergistic mode of action against trypomastigotes in combination with the reference drug BZ.

4. EXPERIMENTAL SECTION

4.1 Chemistry

Chemical reagents used for compound synthesis were purchased from: E. Merck (Darmstadt, Germany); Panreac Química S.A. (Montcada I Reixac, Barcelona, Spain); Sigma-Aldrich Química S.A. (Alcobendas, Madrid, Spain); Acros Organics (Janssen Pharmaceuticalaan, Geel, Belgium); abcr GmbH (Karlsruhe, Germany); Fluorochem Ltd. (Hadfield, Derbyshire, United Kingdom). The progress of all reactions was monitored by thin layer chromatography (TLC) using SIL G/UV_{254}, 0.2mm thickness (ALUGRAM® Xtra SIL G, Macherey-Nagel GmbH & Co. KG) as the stationary phase, and solvent mixtures (CH_2Cl_2/methanol or hexane/ethyl acetate) as the mobile phase; UV lamps (254nm) were employed to spots detection. Purification of

compounds was carried out on a CombiFlash® RF instrument (Teledyne Isco), employing Silica RediSep Rf Gold® columns in a normal phase gradient. Infrared spectra (IR) were recorded on a Thermo Nicolet FT-IR Nexus spectrophotometer using potassium bromide (KBr) pellets for solid samples. IR absorption pics signals (cm^{-1}) were expressed as strong (s), medium (m), and weak (w). Proton (^{1}H) and carbon (^{13}C) NMR spectra of every compound were recorded on a Bruker Advance Neo 400 Ultrashield™ spectrometer (Rheinstetten, Germany) operating at 400/100 MHz ($^{1}H/^{13}C$) and using DMSO-d_6 as solvent and tetramethylsilane (TMS) as reference. Chemical shifts (δ) were reported in parts per million (ppm), coupling constants (*J*) were given in hertz (Hz) and multiplicities detected in ^{1}H-RMN. Elemental analysis was performed on a LECO CHN-900 Elemental Analyzer (Leco, Tres Cantos, Spain). Purity of compounds was confirmed when elemental analysis values were within the range of ± 0.4 with respect to theoretical values. Melting points (Mp) were determined on a Mettler FP82 + FP80 apparatus (Greifensee, Switzerland). High-resolution mass spectrometry data were obtained using G220 Accurate-Mass TOF LC/MS (time of flight analyzer) and HPLC 1200 series Agilent® Technologies.

4.2 General Procedure for the Synthesis of Compounds

4.2.1 Synthesis of the intermediate compounds (i1)

To a solution of the corresponding methyl ketone reagent (1eq) in THF (10mL), the paraformaldehyde (8eq), diisopropylammonium 2,2,2-trifluoroacetate catalyst (1.5eq) and trifluoroacetic acid (0.1eq) were added. The mixture was stirred at reflux for 8 h. New 8eq of paraformaldehyde were added to the mixture at 2 h and 5 h of the reaction. The reaction was monitored by TLC (hexane/ethyl acetate). Following this, the solvent was removed under vacuum by rotatory evaporation. The residue was diluted in diethyl ether and the corresponding vinyl ketone **i1** was isolated by a triple extraction after addition of HCl 1N (25 mL), NaOH 1N (25 mL) and saturated NaCl solution (25 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and the solvent was removed under vacuum.

4.2.2 Synthesis of imidazole (1a-31a) and benzimidazole Mannich bases-type derivatives (1b-17b).

The general procedure for the synthesis of all final compounds was carried out by Michael addition reaction between the previously synthesised vinyl ketones (**i1**) and imidazole/benzimidazole.

To a solution of **i1** (1eq) in THF (20 mL) was added the corresponding amine (1eq) and K_2CO_3 (1.2eq), then stirred at room temperature for 24-72 h. The reaction was monitored by TLC (DCM/methanol). The residue was purified by automated flash chromatography using DCM/methanol gradient solvent. Next, the solvent was removed under vacuum by rotatory

evaporation. The residue was diluted in DCM and the corresponding final compounds were isolated by an extraction after addition of water (25 mL x 3 times). The organic phase was dried over anhydrous Na_2SO_4, filtered and the solvent was removed under vacuum. The final compounds were obtained by precipitation with *n*-hexane.

4.3 Compound Characterisation

*3-(1H-imidazol-1-yl)-1-phenylpropan-1-one (**1a**)*. Yield: 24%. Mp: 96.5-97.5 ºC. IR (KBr) ν cm^{-1}: 1679 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 7.97 (dd, 2H, **H₂+H₆**, $J_{2-3} = J_{6-5} =$ 8.3 Hz, $J_{2-4} = J_{6-4} =$ 1.2 Hz); 7.66 (s, 1H, **H₂'**); 7.64 (td, 1H, **H₄**, $J_{4-3} = J_{4-5} =$ 6.9 Hz, $J_{4-2} = J_{4-6} =$ 1.6 Hz); 7.55-7.51 (m, 2H, **H₃+H₅**); 7.21 (s, 1H, **H₅'**); 6.86 (s, 1H, **H₄'**); 4,33 (t, 2H, **CH₂-N**, $J_{CH2-CH2}$ = 6.8 Hz); 3.60 (t, 2H, **CH₂-CO**, $J_{CH2-CH2} =$ 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 197.71 (**CO**); 137.44 (**C₂'**); 136.23 (**C₁**); 133.47 (**C₄**); 128.74 (2C, **C₂+C₆**); 128.25 (**C₄'**); 127.94 (2C, **C₃+C₅**); 119.42 (**C₅'**); 41.17 (**CH₂-N**); 39.27 (**CH₂-CO**). Anal. Calc. for $C_{12}H_{12}N_2O$: C 71.98%, H 6.04%, N 13.99%. Found: C 71.78%, H 6.29%, N 13.86%.

*1-(4-fluorophenyl)-3-(1H-imidazol-1-yl)-1-phenylpropan-1-one (**2a**)*. Yield: 26%. Mp: 65.0-66.0 ºC. IR (KBr) ν cm^{-1}: 1681 (s, $\nu_{C=O}$), 1226 (s, ν_{C-F}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.06 (dd, 2H, **H₂+H₆**, $J_{2-3} = J_{6-5} =$ 8.8 Hz, $J_{2-F} = J_{6-F} =$ 5.5 Hz); 7.65 (s, 1H, **H₂'**); 7.35 (t, 2H, **H₃+H₅**, $J_{3-2} = J_{5-6} = J_{3-F} = J_{5-F} =$ 8.8 Hz); 7.20 (s, 1H, **H₅'**); 6.86 (s, 1H, **H₄'**); 4.32 (t, 2H, **CH₂-N**, $J_{CH2-CH2} =$ 6.8 Hz); 3.59 (t, 2H, **CH₂-CO**, $J_{CH2-CH2} =$ 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 196.32 (**CO**); 165.16 (d, **C₄**, $^1J =$ 252 Hz); 137.42 (**C₂'**); 133.00 (d, **C₁**, $^4J =$ 2.8 Hz); 130.99 (2C, d, **C₂+C₆**, $^3J =$ 9.5 Hz); 128.25 (**C₄'**); 119.41 (**C₅'**); 115.75 (2C, d, **C₃+C₅**, $^2J =$ 21.9 Hz); 41.13 (**CH₂-N**); 39.23 (**CH₂-CO**). Anal. Calc. for $C_{12}H_{11}FN_2O$: C 66.05%, H 5.08%, N 12.84%. Found: C 65.67%, H 5.37%, N 12.77%.

*1-(4-chlorophenyl)-3-(1H-imidazol-1-yl)propan-1-one (**3a**)*. Yield: 21%. Mp: 105.0-106.0 ºC. IR (KBr) ν cm^{-1}: 1680 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 7.98 (d, 2H, **H₂+H₆**, $J_{2-3} = J_{6-5} =$ 8.6 Hz); 7.65 (s, 1H, **H₂'**); 7.59 (d, 2H, **H₃+H₅**, $J_{3-2} = J_{5-6} =$ 8.6 Hz); 7.20 (s, 1H, **H₅'**); 6.86 (s, 1H, **H₄'**); 4.32 (t, 2H, **CH₂-N**, $J_{CH2-CH2} =$ 6.8 Hz); 3.59 (t, 2H, **CH₂-CO**, $J_{CH2-CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 196.77 (**CO**); 138.39 (**C₄**); 137.42 (**C₂'**); 134.89 (**C₁**); 129.88 (2C, **C₂+C₆**); 128.85 (2C, **C₃+C₅**); 128.26 (**C₄'**); 119.41 (**C₅'**); 41.08 (**CH₂-N**); 39.29 (**CH₂-CO**). Anal. Calc. for $C_{12}H_{11}ClN_2O$: C 61.42%, H 4.72%, N 11.94%. Found: C 61.38%, H 4.95%, N 11.91%.

*3-(1H-imidazol-1-yl)-1-(4-methoxyphenyl)propan-1-one (**4a**)*. Yield: 32%. Mp: 76.5-77.5 ºC. IR (KBr) ν cm^{-1}: 1669 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 7.95 (d, 2H, **H₂+H₆**, $J_{2-3} = J_{6-5} =$ 8.9 Hz); 7.65 (s, 1H, **H₂'**); 7.20 (s, 1H, **H₅'**); 7.04 (d, 2H, **H₃+H₅**, $J_{3-2} = J_{5-6} =$ 8.8 Hz); 6.85 (s, 1H, **H₄'**); 4.30 (t, 2H, **CH₂-N**, $J_{CH2-CH2} =$ 6.8 Hz); 3.83 (s, 3H, **OCH₃**); 3.52 (t, 2H, **CH₂-CO**, $J_{CH2-CH2} =$ 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 195.98 (**CO**); 163.32

(**C₄**); 137.41 (**C₂'**); 130.29 (2C, **C₂+C₆**); 129.24 (**C₁**); 128.23 (**C₄'**); 119.44 (**C₅'**); 113.92 (2C, **C₃+C₅**); 55.55 (**OCH₃**); 41.31 (**CH₂-N**); 38.89 (**CH₂-CO**). Anal. Calc. for $C_{13}H_{14}N_2O_2$: C 67.81%, H 6.13%, N 12.17%. Found: C 67.84%, H 6.31%, N 12.24%.

*3-(1H-imidazol-1-yl)-1-(4-(trifluoromethyl)phenyl)propan-1-one (**5a**)*. Yield: 25%. Mp: 69.0-69.5 ºC. IR (KBr) ν cm^{-1}: 1683 (s, $\nu_{C=O}$), 1325 (s, ν_{C-F}), 1211 (s, ν_{C-F}), 1164 (s, ν_{C-F}). ^1H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.16 (d, 2H, **H₂+H₆**, $J_{2-3} = J_{6-5} = 8.1$ Hz); 7.90 (d, 2H, **H₃+H₅**, $J_{3-2} = J_{5-6} = 8.3$ Hz); 7.67 (s, 1H, **H₂'**); 7.22 (s, 1H, **H₅'**); 6.87 (s, 1H, **H₄'**); 4.34 (t, 2H, **CH₂-N**, $J_{CH2-CH2} = 6.8$ Hz); 3.67 (t, 2H, **CH₂-CO**, $J_{CH2-CH2} = 6.8$ Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 197.27 (**CO**); 139.32 (**C₁**); 137.45 (**C₂'**); 132.76 (q, **C₄**, $^2J = 32.1$ Hz); 128.80 (2C, **C₂+C₆**), 128.31 (**C₄'**); 125.75 (2C, q, **C₃+C₅**, $^3J = 3.6$ Hz); 123.75 (q, CF_3 $^1J = 272.8$ Hz); 119.43 (**C₅'**); 41.02 (**CH₂-N**); 39.69 (**CH₂-CO**). Anal. Calc. for $C_{13}H_{11}F_3N_2O$: C 58.21%, H 4.13%, N 10.44%. Found: C 58.60%, H 4.46%, N 10.46%.

*3-(1H-imidazol-1-yl)-1-(p-tolyl)propan-1-one (**6a**)*. Yield: 24%. Mp: 55.0-56.0 ºC. IR (KBr) ν cm^{-1}: 1681 (s, $\nu_{C=O}$). ^1H NMR (DMSO-d_6, 400 MHz) δ ppm: 7.87 (d, 2H, **H₂+H₆**, $J_{2-3} = J_{6-5} = 8.2$ Hz); 7.65 (s, 1H, **H₂'**); 7.33 (d, 2H, **H₃+H₅**, $J_{3-2} = J_{5-6} = 8.0$ Hz); 7.20 (s, 1H, **H₅'**); 6.86 (s, 1H, **H₄'**); 4.31 (t, 2H, **CH₂-N**, $J_{CH2-CH2} = 6.8$ Hz); 3.55 (t, 2H, **CH₂-CO**, $J_{CH2-CH2} = 6.8$ Hz); 2.37 (s, 3H, **CH₃**). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 197.18 (**CO**); 143.87 (**C₄**); 137.41 (**C₂'**); 133.80 (**C₁**); 129.27 (2C, **C₃+C₅**); 128.23 (**C₄'**); 128.05 (2C, **C₂+C₆**); 119.41 (**C₅'**); 41.22 (**CH₂-N**); 39.14 (**CH₂-CO**); 21.13 (**CH₃**). Anal. Calc. for $C_{13}H_{14}N_2O$: C 72.87%, H 6.59%, N 13.07%. Found: C 72.72%, H 6.68%, N 13.24%.

*3-(1H-imidazol-1-yl)-1-(4-nitrophenyl)-propan-1-one (**7a**)*. Yield: 42%. Mp: 123.0-124.0 ºC. IR (KBr) ν cm^{-1}: 1682 (s, $\nu_{C=O}$), 1520 (s, ν_{NO2}), 1350 (s, ν_{NO2}). ^1H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.34 (d, 2H, **H₃+H₅**, $J_{3-2} = J_{5-6} = 8.8$ Hz); 8.20 (d, 2H, **H₂+H₆**, $J_{2-3} = J_{6-5} = 8.8$ Hz); 7.67 (s, 1H, **H₂'**); 7.21 (s, 1H, **H₅'**); 6.87 (s, 1H, **H₄'**); 4.34 (t, 2H, **CH₂-N**, $J_{CH2-CH2} = 6.8$ Hz); 3.69 (t, 2H, **CH₂-CO**, $J_{CH2-CH2} = 6.8$ Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 197.02 (**CO**); 150.07 (**C₄**); 140.71 (**C₁**); 137.43 (**C₂'**); 129.40 (2C, **C₂+C₆**); 128.31 (**C₄'**); 123.85 (2C, **C₃+C₅**); 119.41 (**C₅'**); 40.98 (**CH₂-N**); 39.65 (**CH₂-CO**). Anal. Calc. for $C_{12}H_{11}N_3O_3$: C 58.77%, H 4.52%, N 17.13%. Found: C 58.74 %, H % 4.71, N % 16.75.

*3-(1H-imidazol-1-yl)-1-(thiophen-3-yl)propan-1-one (**8a**)*. Yield: 45%. Mp: 86.5-87.0 ºC. IR (KBr) ν cm^{-1}: 1659 (s, $\nu_{C=O}$). ^1H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.53 (dd, 1H, **H₂**, $J_{2-5} = 2.8$ Hz, $J_{2-4} = 1.3$ Hz); 7.64 (s, 1H, **H₂'**); 7.63 (dd, 1H, **H₅**, $J_{5-4} = 5.1$ Hz, $J_{5-2} = 2.8$ Hz); 7.51 (dd, 1H, **H₄**, $J_{4-5} = 5.1$ Hz, $J_{4-2} = 1.3$ Hz); 7.19 (s, 1H, **H₅'**); 6.86 (s, 1H, **H₄'**); 4.30 (t, 2H, **CH₂-N**, $J_{CH2-CH2} = 6.8$ Hz); 3.48 (t, 2H, **CH₂-CO**, $J_{CH2-CH2} = 6.8$ Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 192.01 (**CO**); 141.52 (**C₃**); 137.14 (**C₂'**); 134.12 (**C₂**); 128.27 (**C₄'**); 127.59 (**C₅**); 126.37 (**C₄**); 119.40 (**C₅'**); 41.07 (**CH₂-N**); 40.31 (**CH₂-CO**). Anal. Calc. for $C_{10}H_{10}N_2OS$: C 58.23%, H 4.89%, N 13.58%. Found: C 57.93%, H 4.97%, N 13.64%.

*3-(1H-imidazol-1-yl)-1-(thiophen-2-yl)propan-1-one (**9a**)*. Yield: 45%. Mp: 75.5-76.0 ºC. IR (KBr) ν cm^{-1}: 1673 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.02 (dd, 1H, **H$_5$**, J_{5-4} = 4.9 Hz, J_{5-3} = 1.1 Hz); 7.98 (dd, 1H, **H$_3$**, J_{3-4} = 3.8 Hz, J_{3-5} = 1.1 Hz); 7.64 (s, 1H, **H$_{2'}$**); 7.24 (dd, 1H, **H$_4$**, J_{4-5} = 4.9 Hz, J_{4-3} = 3.8 Hz); 7.19 (s, 1H, **H$_{5'}$**); 6.85 (s, 1H, **H$_{4'}$**); 4.31 (t, 2H, **CH$_2$-N**, $J_{CH2-CH2}$ = 6.8 Hz); 3.52 (t, 2H, **CH$_2$-CO**, $J_{CH2-CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 190.65 (**CO**); 143.30 (**C$_2$**); 137.40 (**C$_{2'}$**); 135.20 (**C$_5$**); 133.80 (**C$_3$**); 128.78 (**C$_4$**); 128.29 (**C$_{4'}$**); 119.39 (**C$_{5'}$**); 41.16 (**CH$_2$-N**); 39.61 (**CH$_2$-CO**). Anal. Calc. for $C_{10}H_{10}N_2OS$: C 58.23%, H 4.89%, N 13.58%. Found: C 58.04%, H 5.07%, N 14.07%.

*1-(furan-2-yl)-3-(1H-imidazol-1-yl)propan-1-one (**10a**)*. Yield: 21%. Mp: 92.0-93.0 ºC. IR (KBr) ν cm^{-1}: 1684 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 7.99 (dd, 1H, **H$_5$**, J_{5-4} = 1.6 Hz, J_{5-3} = 0.6 Hz); 7.62 (s, 1H, **H$_{2'}$**); 7.50 (dd, 1H, **H$_3$**, J_{3-4} = 3.6 Hz, J_{3-5} = 0.5 Hz); 7.17 (s, 1H, **H$_{5'}$**); 6.85 (s, 1H, **H$_{4'}$**); 6.71 (dd, 1H, **H$_4$**, J_{4-3} = 3.6 Hz, J_{4-5} = 1.7 Hz); 4.30 (t, 2H, **CH$_2$-N**, $J_{CH2-CH2}$ = 6.8 Hz); 3.37 (t, 2H, **CH$_2$-CO**, $J_{CH2-CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 185.78 (**CO**); 151.57 (**C$_2$**); 148.04 (**C$_5$**); 137.39 (**C$_{2'}$**); 128.31 (**C$_{4'}$**); 119.35 (**C$_{5'}$**); 119.03 (**C$_3$**); 112.55 (**C$_4$**); 40.89 (**CH$_2$-N**); 38.96 (**CH$_2$-CO**). Anal. Calc. for $C_{10}H_{10}N_2O_2$: C 63.15%, H 5.30%, N 14.73%. Found: C 63.35%, H 5.29%, N 15.11%.

*3-(1H-imidazol-1-yl)-1-(naphthalene-2-yl)propan-1-one (**11a**)*. Yield: 24%. Mp: 110.5-111.5 ºC. IR (KBr) ν cm^{-1}: 1682 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.70 (s, 1H, **H$_1$**); 8.12 (d, 1H, **H$_3$**, J_{3-4} = 7.9 Hz); 8.03-7.97 (m, 3H, **H$_4$ + H$_6$ + H$_9$**); 7.71 (s, 1H, **H$_{2'}$**); 7.70-7.61 (m, 2H, **H$_8$ + H$_7$**); 7.25 (s, 1H, **H$_{5'}$**); 6.88 (s, 1H, **H$_{4'}$**); 4.39 (t, 2H, **CH$_2$-N**, $J_{CH2-CH2}$ = 6.9 Hz); 3.74 (t, 2H, **CH$_2$-CO**, $J_{CH2-CH2}$ = 6.9 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 197.62 (**CO**); 137.44 (**C$_{2'}$**); 135.14 (**C$_5$**); 133.50 (**C$_{10}$**); 132.15 (**C$_2$**); 130.14 (**C$_1$**); 129.60 (**C$_3$**); 128.76 (**C$_7$**); 128.33 (**C$_{4'}$**); 128.21 (**C$_8$**); 127.67 (**C$_9$**); 126.98 (**C$_4$**); 123.31 (**C$_6$**); 119.49 (**C$_{5'}$**); 41.35 (**CH$_2$-N**); 39.42 (**CH$_2$-CO**). Anal. Calc. for $C_{16}H_{14}N_2O$: C 76.78%, H 5.64%, N 11.19%. Found: C 76.63%, 5.47H %, N 11.06%.

*1-(benzo[b]thiophen-3-yl)-3-(1H-imidazol-1-yl)propan-1-one (**12a**)*. Yield: 33%. Mp: 105.0-106.0 ºC. IR (KBr) ν cm^{-1}: 1666 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 9.00 (s, 1H, **H$_2$**); 8.61 (dd, 1H, **H$_5$**, J_{5-6} = 8.0 Hz, J_{5-8} = 0.7 Hz); 8.08 (dd, 1H, **H$_8$**, J_{8-7} = 7.9 Hz, J_{8-5} = 0.5 Hz); 7.68 (s, 1H, **H$_{2'}$**); 7.53-7.44 (m, 2H, **H$_6$+H$_7$**); 7.23 (s, 1H, **H$_{5'}$**); 6.87 (s, 1H, **H$_{4'}$**); 4.37 (t, 2H, **CH$_2$-N**, $J_{CH2-CH2}$ = 6.8 Hz); 3.62 (t, 2H, **CH$_2$-CO**, $J_{CH2-CH2}$ = 6.9 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 193.12 (**CO**); 140.21 (**C$_2$**); 139.35 (**C$_3$**); 137.42 (**C$_{2'}$**); 136.07 (**C$_4$**); 133.82 (**C$_9$**); 128.29 (**C$_{4'}$**); 125.82 (**C$_6$**); 125.40 (**C$_7$**); 124.61 (**C$_5$**); 122.91 (**C$_8$**); 119.43 (**C$_{5'}$**); 41.25 (**CH$_2$-N**); 40.67 (**CH$_2$-CO**). Anal. Calc. for $C_{14}H_{12}N_2OS$: C 65.60%, H 4.72%, N 10.93%. Found: C 65.75%, H 5.03%, N 10.86%.

*1-(benzo[b]thiophen-2-yl)-3-(1H-imidazol-1-yl)propan-1-one (**13a**)*. Yield: 31%. Mp: 149.0-150.0 ºC. IR (KBr) ν cm^{-1}: 1660 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.40 (s, 1H, **H$_3$**); 8.05 (d, 1H, **H$_8$**, J_{8-7} = 8.1 Hz); 8.01 (d, 1H, **H$_5$**, J_{5-6} = 7.8 Hz); 7.67 (s, 1H, **H$_{2'}$**); 7.54

(t, 1H, **H$_6$**, $J_{6-5} = J_{6-7} = 7.1$ Hz); 7.47 (t, 1H, **H$_7$**, $J_{7-8} = J_{7-6} = 7.2$ Hz); 7.23 (s, 1H, **H$_{5'}$**); 6.87 (s, 1H, **H$_{4'}$**); 4.36 (t, 2H, **CH$_2$-N**, $J_{CH2-CH2} = 6.8$ Hz); 3.66 (t, 2H, **CH$_2$-CO**, $J_{CH2-CH2} = 6.8$ Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 192.42 (**CO**); 142.58 (**C$_9$**); 141.52 (**C$_4$**); 139.04 (**C$_2$**); 137.42 (**C$_{2'}$**); 131.26 (**C$_3$**); 128.33 (**C$_{4'}$**); 127.84 (**C$_6$**); 126.35 (**C$_5$**); 125.30 (**C$_7$**); 123.15 (**C$_8$**); 119.39 (**C$_{5'}$**); 41.18 (**CH$_2$-N**); 39.61 (**CH$_2$-CO**). Anal. Calc. for $C_{14}H_{12}N_2OS$: C 65.60%, H 4.72%, N 10.93%. Found: C 65.66%, H 5.07%, N 10.74%.

*1-(benzofuran-2-yl)-3-(1H-imidazol-1-yl)propan-1-one (**14a**)*. Yield: 26%. Mp: 131.0-132.0 ºC. IR (KBr) ν cm^{-1}: 1677 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 7.95 (d, 1H, **H$_3$**, $J_{3-5} = 0.7$ Hz); 7.83 (d, 1H, **H$_5$**, $J_{5-6} = 7.8$ Hz); 7.71 (dd, 1H, **H$_8$**, $J_{8-7} = 8.4$ Hz, $J_{8-6} = 0.6$ Hz); 7.66 (s, 1H, **H$_{2'}$**); 7.54 (td, 1H, **H$_7$**, $J_{7-8} = 8.4$ Hz, $J_{7-6} = 7.3$ Hz, $J_{7-5} = 1.2$ Hz); 7.37 (t, 1H, **H$_6$**, $J_{6-5} = J_{6-7} = 7.9$ Hz); 7.21 (s, 1H, **H$_{5'}$**); 6.86 (s, 1H, **H$_{4'}$**); 4.36 (t, 2H, **CH$_2$-N**, $J_{CH2-CH2} = 6.8$ Hz); 3.54 (t, 2H, **CH$_2$-CO**, $J_{CH2-CH2} = 6.8$ Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 187.97 (**CO**); 155.00 (**C$_9$**); 151.62 (**C$_2$**); 137.43 (**C$_{2'}$**); 128.67 (**C$_7$**); 128.35 (**C$_{4'}$**); 126.68 (**C$_4$**); 124.11 (**C$_6$**); 123.75 (**C$_5$**); 119.39 (**C$_{5'}$**); 114.59 (**C$_3$**); 112.26 (**C$_8$**); 40.91 (**CH$_2$-N**); 39.46 (**CH$_2$-CO**). Anal. Calc. for $C_{14}H_{12}N_2O_2$: C 69.99%, H 5.03%, N 11.66%. Found: C 70.35%, H 5.25%, N 11.63%.

*1-(4-bromophenyl)-3-(1H-imidazol-1-yl)propan-1-one (**15a**)*. Yield: 23%. Mp: 95.5-96.5 ºC. IR (KBr) ν cm^{-1}: 1686 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 7.91 (d, 2H, **H$_2$+H$_6$**, $J_{2-3} = J_{6-5} = 8.6$ Hz); 7.74 (d, 2H, **H$_3$+H$_5$**, $J_{3-2} = J_{5-6} = 8.6$ Hz); 7.66 (s, 1H, **H$_{2'}$**); 7.21 (s, 1H, **H$_{5'}$**); 6.86 (s, 1H, **H$_{4'}$**); 4.32 (t, 2H, **CH$_2$-N**, $J_{CH2-CH2} = 6.8$ Hz); 3.59 (t, 2H, **CH$_2$-CO**, $J_{CH2-CH2} = 6.8$ Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 196.98 (**CO**); 137.43 (**C$_{2'}$**); 135.19 (**C$_1$**); 131.81 (2C, **C$_3$+C$_5$**); 129.98 (2C, **C$_2$+C$_6$**); 128.27 (**C$_{4'}$**); 127.61 (**C$_4$**); 119.42 (**C$_{5'}$**); 41.08 (**CH$_2$-N**); 39.31 (**CH$_2$-CO**). Anal. Calc. for $C_{12}H_{11}BrN_2O$: C 51.63%, H 3.97%, N 10.04%. Found: C 52.01%, H 4.01%, N 10.03%.

*3-(1H-imidazol-1-yl)-1-(4-(trifluoromethoxy)phenyl)propan-1-one (**16a**)*. Yield: 23%. Mp: 45.0-46.0 ºC. IR (KBr) ν cm^{-1}: 1691 (s, $\nu_{C=O}$), 1265 (s, ν_{C-F}), 1213 (s, ν_{C-F}), 1161 (s, ν_{C-F}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.11 (d, 2H, **H$_2$+H$_6$**, $J_{2-3} = J_{6-5} = 8.9$ Hz); 7.66 (s, 1H, **H$_{2'}$**); 7.51 (d, 2H, **H$_3$+H$_5$**, $J_{3-2} = J_{5-6} = 8.0$ Hz); 7.20 (s, 1H, **H$_{5'}$**); 6.86 (s, 1H, **H$_{4'}$**); 4.32 (t, 2H, **CH$_2$-N**, $J_{CH2-CH2} = 6.8$ Hz); 3.62 (t, 2H, **CH$_2$-CO**, $J_{CH2-CH2} = 6.8$ Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 196.57 (**CO**); 151.72 (**C$_4$**); 137.45 (**C$_{2'}$**); 135.07 (**C$_1$**); 130.52 (2C, **C$_2$+C$_6$**); 128.29 (**C$_{4'}$**); 120.80 (2C, **C$_3$+C$_5$**); 119.93 (q, **CF$_3$**, $^1J = 262.7$ Hz); 119.43 (**C$_{5'}$**); 41.07 (**CH$_2$-N**); 39.40 (**CH$_2$-CO**). Anal. Calc. for $C_{13}H_{11}F_3N_2O_2$: C 54.93%, H 3.90%, N 9.86%. Found: C 54.8%, H 3.85%, N 9.9%.

*4-(3-(1H-imidazol-1-yl)propanoyl)benzonitrile (**17a**)*. Yield: 30%. Mp: 110.0-111.0 ºC. IR (KBr) ν cm^{-1}: 2230 (s, $\nu_{C\equiv N}$), 1685 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.11 (d, 2H, **H$_2$+H$_6$**, $J_{2-3} = J_{6-5} = 8.6$ Hz); 8.01 (d, 2H, **H$_3$+H$_5$**, $J_{3-2} = J_{5-6} = 8.5$ Hz); 7.66 (s, 1H, **H$_{2'}$**); 7.20 (s, 1H, **H$_{5'}$**); 6.86 (s, 1H, **H$_{4'}$**); 4.33 (t, 2H, **CH$_2$-N**, $J_{CH2-CH2} = 6.8$ Hz); 3.66 (t, 2H, **CH$_2$-CO**, J_{CH2-}

$_{CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 197.23 (**CO**); 139.28 (**C$_1$**); 137.43 (**C$_{2'}$**); 132.81 (2C, **C$_3$+C$_5$**); 128.58 (2C, **C$_2$+C$_6$**); 128.29 (**C$_{4'}$**); 119.41 (**C$_{5'}$**); 118.10 (**CN**); 115.39 (**C$_4$**); 40.98 (**CH$_2$-N**); 39.64 (**CH$_2$-CO**). Anal. Calc. for $C_{13}H_{11}N_3O$: C 69.32%, H 4.92%, N 18.66%. Found: C 69.98%, H 5.13%, N 18.31%.

*3-(1H-imidazol-1-yl)-1-(o-tolyl)propan-1-one (**18a**)*. Yield: 30%. Mp: 53.5-54.5 ºC. IR (KBr) ν cm^{-1}: 1668 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 7.77 (d, 1H, **H$_6$**, $J_{6\text{-}5}$ = 7.7 Hz); 7.65 (s, 1H, **H$_{2'}$**); 7.44 (t, 1H, **H$_4$**, $J_{4\text{-}3}$ = $J_{4\text{-}5}$ = 7.5 Hz); 7.44 (m, 2H, **H$_3$+H$_5$**, $J_{3\text{-}4}$ = $J_{5\text{-}4}$ = 7.5 Hz); 7.20 (s, 1H, **H$_{5'}$**); 6.87 (s, 1H, **H$_{4'}$**); 4.31 (t, 2H, **CH$_2$-N**, $J_{CH2\text{-}CH2}$ = 6.7 Hz); 3.50 (t, 2H, **CH$_2$-CO**, $J_{CH2\text{-}CH2}$ = 6.7 Hz); 2.36 (s, 3H, **CH$_3$**). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 201.51 (**CO**); 137.42 (**C$_{2'}$**); 137.20 (**C$_1$**); 137.13 (**C$_2$**); 131.66 (**C$_3$**); 131.57 (**C$_4$**); 128.79 (**C$_6$**); 128.28 (**C$_{4'}$**); 125.93 (**C$_5$**); 119.35 (**C$_{5'}$**); 41.93 (**CH$_2$-N**); 41.34 (**CH$_2$-CO**); 20.64 (**CH$_3$**). Anal. Calc. for $C_{13}H_{14}N_2O$: C 72.87%, H 6.59%, N 13.07%. Found: C 72.96%, H 6.37%, N 12.94%.

*3-(1H-imidazol-1-yl)-1-(3-nitrophenyl)-propan-1-one (**19a**)*. Yield: 44%. Mp: 83.5-84.5 ºC. IR (KBr) ν cm^{-1}: 1686 (s, $\nu_{C=O}$), 1526 (s, ν_{NO2}), 1359 (s, ν_{NO2}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.66 (s, 1H, **H$_2$**); 8.47 (d, 1H, **H$_4$**, $J_{4\text{-}5}$ = 8.2 Hz, $J_{4\text{-}2}$ = $J_{4\text{-}6}$ = 1.4 Hz); 8.39 (d, 1H, **H$_6$**, $J_{6\text{-}5}$ = 7.8 Hz); 7.83 (t, 1H, **H$_5$**, $J_{5\text{-}4}$ = $J_{5\text{-}6}$ = 8.0 Hz) 7.68 (s, 1H, **H$_{2'}$**); 7.22 (s, 1H, **H$_{5'}$**); 6.87 (s, 1H, **H$_{4'}$**); 4.36 (t, 2H, **CH$_2$-N**, $J_{CH2\text{-}CH2}$ = 6.7 Hz); 3.73 (t, 2H, **CH$_2$-CO**, $J_{CH2\text{-}CH2}$ = 6.7 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 196.83 (**CO**); 148.53 (**C$_3$**); 137.93 (**C$_{2'}$**); 137.80 (**C$_1$**); 134.64 (**C$_6$**); 131.09 (**C$_5$**); 128.74 (**C$_{4'}$**); 128.11 (**C$_4$**); 122.81 (**C$_2$**); 119.93 (**C$_{5'}$**); 41.44 (**CH$_2$-N**); 40.07 (**CH$_2$-CO**). Anal. Calc. for $C_{12}H_{11}N_3O_3$: C 58.77%, H 4.52%, N 17.13%. Found: C 58.49%, H 4.61%, N 16.98%.

*1-(3,4-difluorophenyl)-3-(1H-imidazol-1-yl)propan-1-one (**20a**)*. Yield: 24%. Mp: 95.5-96.5 ºC. IR (KBr) ν cm^{-1}: 1682 (s, $\nu_{C=O}$), 1284 (s, $\nu_{C\text{-}F}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.02 (ddd, 1H, **H$_2$**, $J_{2\text{-}F}$ = 11.3 Hz, $J_{2\text{-}F'}$ = 7.9 Hz, $J_{2\text{-}6}$ = 2.1 Hz); 7.86-7.90 (m, 1H, **H$_6$**); 7.65 (s, 1H, **H$_{2'}$**); 7.60 (dt, 1H, **H$_5$**, $J_{5\text{-}F}$ = 10.4 Hz, $J_{5\text{-}F'}$ = $J_{5\text{-}6}$ = 8.4 Hz); 7.20 (s, 1H, **H$_{5'}$**); 6.86 (s, 1H, **H$_{4'}$**); 4.31 (t, 2H, **CH$_2$-N**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 3.60 (t, 2H, **CH$_2$-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 195.67 (**CO**); 152.75 (dd, **C$_3$**, ^1J = 253.8 Hz, ^2J = 12.8 Hz); 149.47 (dd, **C$_4$**, *1J* = 247.9 Hz, ^2J = 13.1 Hz); 137.41 (**C$_{2'}$**); 133.72 (**C$_1$**); 128.27 (**C$_{4'}$**); 125.82 (dd, **C$_6$**, ^3J = 7.9 Hz, ^4J = 3.5 Hz); 119.40 (**C$_{5'}$**); 117.98 (d, **C$_5$**, ^2J = 17.9 Hz); 117.35 (d, **C$_2$**, ^2J = 18.1 Hz); 41.04 (**CH$_2$-N**); 39.31 (**CH$_2$-CO**). Anal. Calc. for $C_{12}H_{10}F_2N_2O$: C 61.02%, H 4.27%, N 11.86%. Found: C 61.31%, H 4.4%, N 11.84%.

*1-(4-chloro-3-fluorophenyl)-3-(1H-imidazol-1-yl)propan-1-one (**21a**)*. Yield: 21%. Mp: 110.0-111.0 ºC. IR (KBr) ν cm^{-1}: 1682 (s, $\nu_{C=O}$), 1229 (s, $\nu_{C\text{-}F}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 7.96 (dd, 1H, **H$_2$**, $J_{2\text{-}F}$ = 10.1 Hz, $J_{2\text{-}6}$ = 1.9 Hz); 7.83 (dd, 1H, **H$_6$**, $J_{6\text{-}5}$ = 8.5 Hz, $J_{6\text{-}2}$ = 1.8 Hz); 7.77 (dd, 1H, **H$_5$**, $J_{5\text{-}6}$ = 7.2 Hz, $J_{5\text{-}F}$ = 5.5 Hz); 7.65 (s, 1H, **H$_{2'}$**); 7.20 (s, 1H, **H$_{5'}$**); 6.86 (s, 1H, **H$_{4'}$**); 4.32 (t, 2H, **CH$_2$-N**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 3.61 (t, 2H, **CH$_2$-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 196.01 (d, **CO**, ^4J = 1.8 Hz); 157.25 (d, **C$_3$**, ^1J = 248.2 Hz);

137.41 (**C$_{2'}$**); 136.89 (d, **C$_1$**, ^3J = 5.6 Hz); 131.17 (**C$_5$**); 128.28 (**C$_{4'}$**); 125.17 (d, **C$_6$**, ^4J = 3.6 Hz); 124.99 (d, **C$_4$**, ^2J = 17.6 Hz); 119.40 (**C$_{5'}$**); 116.12 (d, **C$_2$**, ^2J = 21.9 Hz); 41.00 (**CH$_2$-N**); 39.42 (**CH$_2$-CO**). Anal. Calc. for $C_{12}H_{10}ClFN_2O$: C 57.04%, H 3.99%, N 11.09%. Found: C 57.18%, H 4.05%, N 11.16%.

*1-(3-chloro-4-fluorophenyl)-3-(1H-imidazol-1-yl)propan-1-one (**22a**)*. Yield: 26%. Mp: 94.0-95.0 ºC. IR (KBr) ν cm^{-1}: 1687 (s, $\nu_{C=O}$), 1248 (s, ν_{C-F}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.18 (dd, 1H, **H$_2$**, J_{2-F} = 7.2 Hz, J_{2-6} = 2.2 Hz); 8.00 (ddd, 1H, **H$_6$**, J_{6-5} = 8.6 Hz, J_{6-F} = 4.8 Hz, J_{6-2} = 2.2 Hz); 7.65 (s, 1H, **H$_{2'}$**); 7.58 (t, 1H, **H$_5$**, J_{5-F} = J_{5-6} = 8.9 Hz); 7.20 (s, 1H, **H$_{5'}$**); 6.86 (s, 1H, **H$_{4'}$**); 4.31 (t, 2H, **CH$_2$-N**, $J_{CH2-CH2}$ = 6.8 Hz); 3.62 (t, 2H, **CH$_2$-CO**, $J_{CH2-CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 195.64 (**CO**); 160.19 (d, **C$_4$**, ^1J = 254.0 Hz); 137.41 (**C$_{2'}$**); 133.94 (d, **C$_1$**, ^4J = 3.5 Hz); 130.75 (**C$_2$**); 129.30 (d, **C$_6$**, ^3J = 8.8 Hz); 128.25 (**C$_{4'}$**); 120.30 (d, **C$_3$**, ^2J = 18.2 Hz); 119.41 (**C$_{5'}$**); 117.36 (d, **C$_5$**, ^2J = 21.5 Hz); 41.03 (**CH$_2$-N**); 39.28 (**CH$_2$-CO**). Anal. Calc. for $C_{12}H_{10}ClFN_2O$: C 57.04%, H 3.99%, N 11.09%. Found: C 56.87%, H 4.14%, N 11.14%.

*1-(3-bromo-4-fluorophenyl)-3-(1H-imidazol-1-yl)propan-1-one (**23a**)*. Yield: 26%. Mp: 118.5-119.5 ºC. IR (KBr) ν cm^{-1}: 1686 (s, $\nu_{C=O}$), 1245 (s, ν_{C-F}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.29 (dd, 1H, **H$_2$**, J_{2-F} = 6.7 Hz, J_{2-6} = 2.1 Hz); 8.03 (ddd, 1H, **H$_6$**, J_{6-5} = 8.6 Hz, J_{6-F} = 4.9 Hz, J_{6-2} = 2.2 Hz); 7.65 (s, 1H, **H$_{2'}$**); 7.53 (t, 1H, **H$_5$**, J_{5-F} = J_{5-6} = 8.6 Hz); 7.20 (s, 1H, **H$_{5'}$**); 6.86 (s, 1H, **H$_{4'}$**); 4.31 (t, 2H, **CH$_2$-N**, $J_{CH2-CH2}$ = 6.8 Hz); 3.62 (t, 2H, **CH$_2$-CO**, $J_{CH2-CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 195.56 (**CO**); 161.24 (d, **C$_4$**, ^1J = 252.3 Hz); 137.41 (**C$_{2'}$**); 134.24 (d, **C$_1$**, ^4J = 3.4 Hz); 133.63 (d, **C$_2$**, ^3J = 1.2 Hz); 129.95 (d, **C$_6$**, ^3J = 8.9 Hz); 128.25 (**C$_{4'}$**); 119.41 (**C$_{5'}$**); 117.14 (d, **C$_5$**, ^2J = 22.8 Hz); 108.74 (d, **C$_3$**, ^2J = 21.7 Hz); 41.03 (**CH$_2$-N**); 39.26 (**CH$_2$-CO**). Anal. Calc. for $C_{12}H_{10}BrFN_2O$: C 48.51%, H 3.39%, N 9.43%. Found: C 48.84%, H 3.70%, N 9.49%.

*1-(3,4-dimethoxyphenyl)3-(1H-imidazol-1-yl)propan-1-one (**24a**)*. Yield: 23%. Mp: 149.0-150.0 ºC. IR (KBr) ν cm^{-1}: 1671 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 7.64 (m, 2H, **H$_{2'}$+H$_2$**); 7.45 (d, 1H, **H$_6$**, J_{6-2} = 2.0 Hz); 7.20 (s, 1H, **H$_{5'}$**); 7.06 (d, 2H, **H$_5$**, J_{5-6} = 8.5 Hz); 6.85 (s, 1H, **H$_{4'}$**); 4.31 (t, 2H, **CH$_2$-N**, $J_{CH2-CH2}$ = 6.8 Hz); 3.84 (s, 3H, **OCH$_3$**); 3.81 (s, 3H, **OCH$_3$**); 3.53 (t, 2H, **CH$_2$-CO**, $J_{CH2-CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 196.07 (**CO**); 153.29 (**C$_4$**); 148.58 (**C$_3$**); 137.45 (**C$_{2'}$**); 129.21 (**C$_1$**); 128.22 (**C$_{4'}$**); 122.74 (**C$_2$**); 119.47 (**C$_{5'}$**); 110.89 (**C$_5$**); 110.16 (**C$_6$**); 55.76 (**C$_2$**); 55.52 (**C$_1$**); 41.38 (**CH$_2$-N**); 38.84 (**CH$_2$-CO**). Anal. Calc. for $C_{14}H_{16}N_2O_3$: C 64.60%, H 6.20%, N 10.76%. Found: C 64.33%, H 6.33%, N 10.74%.

*1-(2,4-dimethoxyphenyl)3-(1H-imidazol-1-yl)propan-1-one (**25a**)*. Yield: 25%. Mp: 58.0-59.0 ºC. IR (KBr) ν cm^{-1}: 1673 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 7.67 (d, 1H, **H$_6$**, J_{6-5} = 8.7 Hz), 7.61 (s, 1H, **H$_{2'}$**); 7.15 (s, 1H, **H$_{5'}$**); 6.84 (s, 1H, **H$_{4'}$**); 6.65-6.60 (m, 2H, **H$_5$+H$_3$**); 4.27 (t, 2H, **CH$_2$-N**, $J_{CH2-CH2}$ = 6.8 Hz); 3.87 (s, 3H, **OCH$_3$**); 3.83 (s, 3H, **OCH$_3$**); 3.38

(t, 2H, **CH_2-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 196.19 (**CO**); 164.57 (**C_4**); 160.97 (**C_2**); 137.40 (**$C_{2'}$**); 131.91 (**C_6**); 128.21 (**$C_{4'}$**); 119.59 (**$C_{5'}$**); 119.43 (**C_1**); 106.16 (**C_5**); 98.45 (**C_3**); 55.91 (**OCH_3**); 55.65 (**OCH_3**); 44.42 (**CH_2-N**); 41.49 (**CH_2-CO**). Anal. Calc. for $C_{14}H_{16}N_2O_3$: C 64.60%, H 6.20%, N 10.76%. Found: C 64.78%, H 6.02%, N 10.61%.

*1-(3,5-dimethoxyphenyl)-3-(1H-imidazol-1-yl)-propan-1-one (**26a**)*. Yield: 32%. Mp: 93.0-94.0 ºC. IR (KBr) ν cm^{-1}: 1675 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 7.65 (s, 1H, **$H_{2'}$**); 7.20 (s, 1H, **$H_{5'}$**); 7.08 (d, 2H, **H_2+H_6**, $J_{2\text{-}4} = J_{6\text{-}4}$ = 2.3 Hz); 6.86 (s, 1H, **$H_{4'}$**); 6.77 (t, 1H, **H_4**, $J_{4\text{-}2} = J_{2\text{-}6}$ = 2.3 Hz); 4.31 (t, 2H, **CH_2-N**, $J_{CH2\text{-}CH2}$ = 6.7 Hz); 3.80 (s, 6H, **OCH_3**); 3.58 (t, 2H, **CH_2-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 197.40 (**CO**); 160.59 (2C, **C_3+C_5**); 138.27 (**C_1**); 137.44 (**$C_{2'}$**); 128.21 (**$C_{4'}$**); 119.45 (**$C_{5'}$**); 105.69 (2C, **C_2+C_6**); 105.35 (**C_4**); 55.52 (2C, **C_1+C_2**); 41.19 (**CH_2-N**); 39.39 (**CH_2-CO**). Anal. Calc. for $C_{14}H_{16}N_2O_3$: C 64.60%, H 6.20%, N 10.76%. Found: C 64.33%, H 6.33%, N 10.74%.

*3-(1H-imidazol-1-yl)-1-(3,4,5-trimethoxyphenyl)propan-1-one (**27a**)*. Yield: 38%. Mp: 122.0-123.0 ºC. IR (KBr) ν cm^{-1}: 1669 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 7.67 (s, 1H, **$H_{2'}$**); 7.26 (s, 2H, **H_2+H_6**); 7.21 (s, 1H, **$H_{5'}$**); 6.87 (s, 1H, **$H_{4'}$**); 4.32 (t, 2H, **CH_2-N**, $J_{CH2\text{-}CH2}$ = 6.7 Hz); 3.85 (s, 6H, **OCH_3**); 3.74 (s, 3H, **OCH_3**); 3.59 (t, 2H, **CH_2-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 196.59 (**CO**); 152.78 (2C, **C_3+C_5**); 142.08 (**C_4**); 137.44 (**$C_{2'}$**); 131.57 (**C_1**); 128.16 (**$C_{4'}$**); 119.52 (**$C_{5'}$**); 105.57 (2C, **C_2+C_6**); 60.15 (**C_2**); 56.08 (2C, **C_1+C_3**); 41.33 (**CH_2-N**); 38.88 (**CH_2-CO**). Anal. Calc. for $C_{15}H_{18}N_2O_4$: C 62.06%, H 6.25%, N 9.65%. Found: C 61.94%, H 6.14%, N 9.57%.

*1-(4-fluoronaphthalen-1-yl)-3-(1H-imidazol-1-yl)-1-propan-1-one (**28a**)*. Yield: 22%. Mp: 60.5-61.5 ºC. IR (KBr) ν cm^{-1}: 1667 (s, $\nu_{C=O}$), 1233 (s, $\nu_{C\text{-}F}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.62 (d, 1H, **H_9**, $J_{9\text{-}8}$ = 8.1 Hz); 8.20 (dd, 1H, **H_2**, $J_{2\text{-}3}$ = 8.2 Hz, $J_{2\text{-}F}$ = 5.6 Hz); 8.13 (d, 1H, **H_6**, $J_{6\text{-}7}$ = 8.8 Hz); 7.75-7.67 (m, 3H, **H_7** + **H_8** + **$H_{2'}$**); 7.44 (dd, 1H, **H_3**, $J_{3\text{-}F}$ = 10.3 Hz, $J_{3\text{-}2}$ = 8.2 Hz); 7.24 (s, 1H, **$H_{5'}$**); 6.88 (s, 1H, **$H_{4'}$**); 4.39 (t, 2H, **CH_2-N**, $J_{CH2\text{-}CH2}$ = 6.7 Hz); 3.69 (t, 2H, **CH_2-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 200.27 (**CO**); 160.22 (d, **C_4**, ^1J = 257.7 Hz); 137.47 (**$C_{2'}$**); 131.44 (d, **C_{10}**, ^3J = 5.2 Hz); 130.97 (d, **C_1**, ^4J = 4.2 Hz); 130.29 (d, **C_2**, ^3J = 10.1 Hz); 129.17 (**C_8**); 128.32 (**$C_{4'}$**); 127.23 (d, **C_7**, ^4J = 1.2 Hz); 125.61 (d, **C_9**, ^4J = 2.2 Hz); 123.12 (d, **C_5**, ^2J = 15.9 Hz); 120.29 (d, **C_6**, ^3J = 6.2 Hz); 119.42 (**$C_{5'}$**); 108.78 (d, **C_3**, ^2J = 20.5 Hz); 42.09 (**CH_2-N**); 41.51 (**CH_2-CO**). Anal. Calc. for $C_{16}H_{13}FN_2O$: C 71.63%, H 4.88%, N 10.44%. Found: C 71.49%, H 4.72%, N 10.67%.

*1-(5-fluorobenzo[b]thiophen-3-yl)-3-(1H-imidazol-1-yl)propan-1-one (**29a**)*. Yield: 18%. Mp: 101.0-102.0 ºC. IR (KBr) ν cm^{-1}: 1654 (s, $\nu_{C=O}$), 1185 (s, $\nu_{C\text{-}F}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 9.10 (s, 1H, **H_2**); 8.29 (dd, 1H, **H_5**, $J_{5\text{-}F}$ = 10.6 Hz, $J_{5\text{-}7}$ = 2.6 Hz); 8.14 (dd, 1H, **H_8**, $J_{8\text{-}7}$ = 8.9, Hz $J_{8\text{-}F}$ = 5.1 Hz); 7.68 (s, 1H, **$H_{2'}$**); 7.37 (td, 1H, **H_7**, $J_{7\text{-}F} = J_{7\text{-}8}$ = 8.9 Hz, $J_{7\text{-}5}$ = 2.6 Hz); 7.22 (s, 1H, **$H_{5'}$**); 6.86 (s, 1H, **$H_{4'}$**); 4.36 (t, 2H, **CH_2-N**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 3.60 (t, 2H, **CH_2-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 193.16 (**CO**); 161.15 (d,

C$_6$, ^1J = 240.4 Hz); 142.88 (**C$_2$**); 137.53 (**C$_{2'}$**); 137.40 (d, **C$_4$**, ^3J = 10.6 Hz); 135.22 (d, **C$_3$**, ^4J = 1.0 Hz); 133.40 (d, **C$_9$**, ^4J = 4.6 Hz); 128.33 (**C$_{4'}$**); 124.86 (d, **C$_8$**, ^3J = 9.7 Hz); 119.58 (**C$_{5'}$**); 114.21 (d, **C$_7$**, ^2J = 25.2 Hz); 110.03 (d, **C$_5$**, ^2J = 24.9 Hz); 41.28 (**CH$_2$-N**); 40.62 (**CH$_2$-CO**). Anal. Calc. for $C_{14}H_{11}FN_2OS$: C 61.30%, H 4.04%, N 10.21%. Found: C 61.27%, H 4.25%, N 10.33%.

*1-(3-benzo[d][1,3]dioxol-5-yl)-3-(1H-imidazol-1-yl)propan-1-one (**30a**)*. Yield: 25%. Mp: 146.0-147.0 ºC. IR (KBr) ν cm^{-1}: 1663 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 7.65 (s, 1H, **H$_{2'}$**); 7.62 (dd, 1H, **H$_7$**, $J_{7\text{-}6}$ = 8.2 Hz, $J_{7\text{-}2}$ = 1.7 Hz); 7.45 (d, 1H, **H$_2$**, $J_{2\text{-}7}$ = 1.6 Hz); 7.20 (s, 1H, **H$_{5'}$**); 7.04 (d, 1H, **H$_6$**, $J_{6\text{-}7}$ = 8.2 Hz); 6.85 (s, 1H, **H$_{4'}$**); 6.13 (s, 2H, **H$_4$**); 4.29 (t, 2H, **CH$_2$-N**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 3.51 (t, 2H, **CH$_2$-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 195.67 (**CO**); 151.66 (**C$_5$**); 147.85 (**C$_3$**); 137.41 (**C$_{2'}$**); 130.95 (**C$_1$**); 128.16 (**C$_{4'}$**); 124.52 (**C$_7$**); 119.46 (**C$_{5'}$**); 108.08 (**C$_2$**); 107.32 (**C$_6$**); 102.08 (**C$_4$**); 41.35 (**CH$_2$-N**); 38.98 (**CH$_2$-CO**). Anal. Calc. for $C_{13}H_{12}N_2O_3$: C 63.93%, H 4.95%, N 11.47%. Found: C 64.11%, H 5.26%, N 11.69%.

*1-(adamantan-1-yl)-3-(1H-imidazol-1-yl)propan-1-one (**31a**)*. Yield: 16%. Mp: 103.0-104.0 ºC. IR (KBr) ν cm^{-1}: 1696 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 7.55 (s, 1H, **H$_{2'}$**); 7.11 (s, 1H, **H$_{5'}$**); 6.83 (s, 1H, **H$_{4'}$**); 4.12 (t, 2H, **CH$_2$-N**, $J_{CH2\text{-}CH2}$ = 6.7 Hz); 3.00 (t, 2H, **CH$_2$-CO**, $J_{CH2\text{-}CH2}$ = 6.7 Hz); 1.95 (s, 3H, **H$_3$ + H$_5$ + H$_8$**); 1.68-1.60 (m, 12H, **H$_2$ + H$_4$ + H$_6$ + H$_7$ + H$_9$ + H$_{10}$**). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 212.52 (**CO**); 137.34 (**C$_{2'}$**); 128.18 (**C$_{4'}$**); 119.28 (**C$_{5'}$**); 45.51 (**C$_1$**); 41.03 (**CH$_2$-N**); 37.15 (3C, **C$_2$+C$_6$+C$_7$**); 36.99 (**CH$_2$-CO**); 35.93 (3C, **C$_4$+C$_9$+C$_{10}$**); 27.26 (3C, **C$_3$+C$_5$+C$_8$**). Anal. Calc. for $C_{16}H_{22}N_2O$: C 74.38%, H 8.58%, N 10.84%. Found: C 74.53%, H 8.41%, N 10.76%.

*1-([1,1'-biphenyl]-4-yl)-3-(1H-imidazol-1-yl)propan-1-one (**32a**)*. Yield: 18%. Mp: 104.0-104.5 ºC. IR (KBr) ν cm^{-1}: (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.05 (d, 2H, **H$_2$ + H$_6$**, $J_{2\text{-}3}$ = $J_{6\text{-}5}$ = 8.4 Hz); 7.82 (d, 2H, **H$_3$ + H$_5$**, $J_{3\text{-}2}$ = $J_{5\text{-}6}$ = 8.4 Hz); 7.74 (d, 2H, **H$_{II}$ + H$_{VI}$**, $J_{II\text{-}III}$ = $J_{VI\text{-}V}$ = 7.2 Hz); 7.68 (s, 1H, **H$_{2'}$**); 7.50 (t, 2H, **H$_{III}$ + H$_V$**, $J_{III\text{-}II}$ = $J_{III\text{-}IV}$ = $J_{V\text{-}IV}$ = $J_{V\text{-}VI}$ = 7.4 Hz); 7.43 (t, 2H, **H$_{IV}$**, $J_{IV\text{-}III}$ = $J_{IV\text{-}V}$ = 7.3 Hz); 7.23 (s, 1H, **H$_{5'}$**); 6.87 (s, 1H, **H$_{4'}$**); 4.35 (t, 2H, **CH$_2$-N**, $J_{CH2\text{-}CH2}$ = 6.7 Hz); 3.62 (t, 2H, **CH$_2$-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 197.28 (**CO**); 144.81 (**C$_4$**); 138.81 (**C$_I$**); 137.48 (**C$_{2'}$**); 135.06 (**C$_1$**); 129.11 (2C, **C$_{III}$+C$_V$**); 128.72 (2C, **C$_2$+C$_6$**); 128.46 (**C$_{IV}$**); 128.28 (**C$_{4'}$**); 127.01 (2C, **C$_{II}$+C$_{VI}$**); 126.92 (2C, **C$_3$+C$_5$**); 119.47 (**C$_{5'}$**); 41.23 (**CH$_2$-N**); 39.06 (**CH$_2$-CO**). Anal. Calc. for $C_{18}H_{16}N_2O$: C 78.24%, H 5.84%, N 10.14%. Found: C 77.99%, H 5.61%, N 10.04%.

*3-(1H-benzo[d]imidazol-1-yl)-1-phenylpropan-1-one (**1b**)*. Yield: 19%. Mp: 90.5-91.5 ºC. IR (KBr) ν cm^{-1}: 1681 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.26 (s, 1H, **H$_{2'}$**); 7.97 (d, 2H, **H$_2$ + H$_6$**, $J_{2\text{-}3}$ = $J_{6\text{-}5}$ = 7.2 Hz); 7.69 (d, 1H, **H$_{8'}$**, $J_{8'\text{-}7'}$ = 7.9 Hz); 7.63 (t, 2H, **H$_{5'}$ + H$_4$**, $J_{5'\text{-}6'}$ = $J_{4\text{-}3}$ = $J_{4\text{-}5}$ = 7.5 Hz); 7.50 (t, 2H, **H$_3$ + H$_5$**, $J_{3\text{-}2}$ = $J_{3\text{-}4}$ = $J_{5\text{-}4}$ = $J_{5\text{-}6}$ = 7.7 Hz); 7.26 (t, 1H, **H$_{7'}$**, $J_{7'\text{-}6'}$ = $J_{7'\text{-}8'}$ = 7.1 Hz); 7.20 (t, 1H, **H$_{6'}$**, $J_{6'\text{-}5'}$ = $J_{6'\text{-}7'}$ = 7.6 Hz); 4.62 (t, 2H, **CH$_2$-N**, $J_{CH2\text{-}CH2}$ = 6.8

Hz); 3.69 (t, 2H, **CH$_2$-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 197.77 (**CO**); 144.22 (**C$_{2'}$**); 143.39 (**C$_{4'}$**); 136.18 (**C$_1$**); 133.72 (**C$_{9'}$**); 133.45 (**C$_4$**); 128.71 (2C, **C$_3$+C$_5$**); 127.94 (2C, **C$_2$+C$_6$**); 122.23 (**C$_{7'}$**); 121.41 (**C$_{6'}$**); 119.35 (**C$_{5'}$**); 110.53 (**C$_{8'}$**); 39.40 (**CH$_2$-N**); 38.01 (**CH$_2$-CO**). HRMS calculated for $C_{16}H_{14}N_2O$: 250.111. Found: 250.123.

*3-(1H-benzo[d]imidazol-1-yl)-1-(4-fluorophenyl)propan-1-one (**2b**)*. Yield: 20%. Mp: 115.5-116.5 ºC. IR (KBr) ν cm^{-1}: 1684 (s, ν$_{C=O}$), 1233 (s, ν$_{C-F}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.25 (s, 1H, **H$_{2'}$**); 8.05 (dd, 2H, **H$_2$ + H$_6$**, $J_{2\text{-}3}$ = $J_{6\text{-}5}$ = 8.9 Hz, $J_{2\text{-}F}$ = $J_{6\text{-}F}$ = 5.6 Hz); 7.68 (d, 1H, **H$_{8'}$**, $J_{8'\text{-}7'}$ = 7.9 Hz); 7.64 (d, 1H, **H$_{5'}$**, $J_{5'\text{-}6'}$ = 7.8 Hz); 7.33 (t, 2H, **H$_3$ + H$_5$**, $J_{3\text{-}2}$ = $J_{3\text{-}F}$ = $J_{5\text{-}F}$ = $J_{5\text{-}6}$ = 8.9 Hz); 7.26 (t, 1H, **H$_{7'}$**, $J_{7'\text{-}6'}$ = $J_{7'\text{-}8'}$ = 7.0 Hz); 7.19 (t, 1H, **H$_{6'}$**, $J_{6'\text{-}5'}$ = $J_{6'\text{-}7'}$ = 7.6 Hz); 4.60 (t, 2H, **CH$_2$-N**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 3.68 (t, 2H, **CH$_2$-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 196.39 (**CO**); 165.14 (d, **C$_4$**, J^1 = 252.1 Hz); 144.20 (**C$_{2'}$**); 143.39 (**C$_{4'}$**); 133.72 (**C$_{9'}$**); 132.96 (d, **C$_1$**, J^4 = 2.7 Hz); 130.99 (2C, **C$_2$+C$_6$**, d, J^3 = 9.5 Hz); 122.21 (**C$_{7'}$**); 121.41 (**C$_{6'}$**); 119.34 (**C$_{5'}$**); 115.71 (d, **C$_3$+C$_5$**, J^2 = 21.9 Hz); 110.53 (**C$_{8'}$**); 39.37 (**CH$_2$-N**); 37.99 (**CH$_2$-CO**). HRMS calculated for $C_{16}H_{13}FN_2O$: 268.108. Found: 268.102.

*3-(1H-benzo[d]imidazol-1-yl)-1-(4-chlorophenyl)propan-1-one (**3b**)*. Yield: 21%. Mp: 131.5-132.0 ºC. IR (KBr) ν cm^{-1}: 1686 (s, ν$_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.25 (s, 1H, **H$_{2'}$**); 7.98 (d, 2H, **H$_2$ + H$_6$**, $J_{2\text{-}3}$ = $J_{6\text{-}5}$ = 8.6 Hz); 7.68 (d, 1H, **H$_{8'}$**, $J_{8'\text{-}7'}$ = 7.9 Hz); 7.64 (d, 1H, **H$_{5'}$**, $J_{5'\text{-}6'}$ = 7.8 Hz); 7.57 (d, 2H, **H$_3$ + H$_5$**, $J_{3\text{-}2}$ = $J_{5\text{-}6}$ = 8.6 Hz); 7.25 (t, 1H, **H$_{7'}$**, $J_{7'\text{-}6'}$ = $J_{7'\text{-}8'}$ = 7.6 Hz); 7.19 (t, 1H, **H$_{6'}$**, $J_{6'\text{-}5'}$ = $J_{6'\text{-}7'}$ = 7.6 Hz); 4.60 (t, 2H, **CH$_2$-N**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 3.68 (t, 2H, **CH$_2$-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 197.04 (**CO**); 144.39 (**C$_{2'}$**); 143.60 (**C$_{4'}$**); 138.56 (**C$_1$**); 135.06 (**C$_4$**); 133.92 (**C$_{9'}$**); 130.08 (2C, **C$_2$+C$_6$**); 129.01 (2C, **C$_3$+C$_5$**); 122.42 (**C$_{7'}$**); 121.61 (**C$_{6'}$**); 119.55 (**C$_{5'}$**); 110.73 (**C$_{8'}$**); 39.52 (**CH$_2$-N**); 38.28 (**CH$_2$-CO**). HRMS calculated for $C_{16}H_{13}ClN_2O$: 285.079. Found: 285.095.

*3-(1H-benzo[d]imidazol-1-yl)-1-(4-methoxyphenyl)propan-1-one (**4b**)*. Yield: 19%. Mp: 95.0-96.0 ºC. IR (KBr) ν cm^{-1}: 1680 (s, ν$_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.25 (s, 1H, **H$_{2'}$**); 7.94 (d, 2H, **H$_2$ + H$_6$**, $J_{2\text{-}3}$ = $J_{6\text{-}5}$ = 8.9 Hz); 7.68 (d, 1H, **H$_{8'}$**, $J_{8'\text{-}7'}$ = 7.9 Hz); 7.63 (d, 1H, **H$_{5'}$**, $J_{5'\text{-}6'}$ = 7.9 Hz); 7.25 (t, 1H, **H$_{7'}$**, $J_{7'\text{-}6'}$ = $J_{7'\text{-}8'}$ = 7.0 Hz); 7.19 (t, 1H, **H$_{6'}$**, $J_{6'\text{-}5'}$ = $J_{6'\text{-}7'}$ = 7.0 Hz); 7.01 (d, 2H, **H$_3$ + H$_5$**, $J_{3\text{-}2}$ = $J_{5\text{-}6}$ = 8.9 Hz); 4.59 (t, 2H, **CH$_2$-N**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 3.82 (s, 3H, **OCH$_3$**); 3.61 (t, 2H, **CH$_2$-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 196.05 (**CO**); 163.31 (**C$_4$**); 144.22 (**C$_{2'}$**); 143.39 (**C$_{4'}$**); 133.72 (**C$_{9'}$**); 130.29 (2C, **C$_2$+C$_6$**); 129.20 (**C$_1$**); 122.20 (**C$_{7'}$**); 121.38 (**C$_{6'}$**); 119.34 (**C$_{5'}$**); 113.88 (2C, **C$_3$+C$_5$**); 110.50 (**C$_{8'}$**); 55.53 (**OCH$_3$**); 39.25 (**CH$_2$-N**); 37.60 (**CH$_2$-CO**). HRMS calculated for $C_{17}H_{16}N_2O_2$: 281.128. Found: 281.141.

*3-(1H-benzo[d]imidazol-1-yl)-1-(4-(trifluoromethyl)phenyl)propan-1-one (**5b**)*. Yield: 22%. Mp: 130.5-131.5 ºC. IR (KBr) ν cm^{-1}: 1689 (s, ν$_{C=O}$), 1335 (s, ν$_{C-F}$), 1294 (s, ν$_{C-F}$), 1160 (s, □$_{C-F}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.27 (s, 1H, **H$_{2'}$**); 8.16 (d, 2H, **H$_2$ + H$_6$**, $J_{2\text{-}3}$ = $J_{6\text{-}5}$ = 8.1 Hz); 7.88 (d, 2H, **H$_3$ + H$_5$**, $J_{3\text{-}2}$ = $J_{5\text{-}6}$ = 8.2 Hz); 7.70 (d, 1H, **H$_{8'}$**, $J_{8'\text{-}7'}$ = 7.8 Hz); 7.64 (d, 1H, **H$_{5'}$**, $J_{5'\text{-}6'}$ = 7.7 Hz); 7.26 (t, 1H, **H$_{7'}$**, $J_{7'\text{-}6'}$ = $J_{7'\text{-}8'}$ = 7.0 Hz); 7.20 (t, 1H, **H$_{6'}$**, $J_{6'\text{-}5'}$ = $J_{6'\text{-}7'}$ = 7.6

Hz); 4.63 (t, 2H, **CH$_2$-N**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 3.76 (t, 2H, **CH$_2$-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 197.32 (**CO**); 144.18 (**C$_{2'}$**); 143.41 (**C$_{4'}$**); 139.29 (**C$_1$**); 133.72 (**C$_{9'}$**); 132.70 (q, **C$_4$**, J^2 = 32.0 Hz); 128.79 (2C, **C$_2$+C$_6$**); 125.68 (2C, **C$_3$+C$_5$**, q, J^3 = 3.7 Hz); 123.72 (q, **CF$_3$**, J^1 = 272.7 Hz); 122.22 (**C$_{7'}$**); 121.42 (**C$_{6'}$**); 119.35 (**C$_{5'}$**); 110.54 (**C$_{8'}$**); 39.25 (**CH$_2$-N**); 38.46 (**CH$_2$-CO**). HRMS calculated for $C_{17}H_{13}F_3N_2O$: 319.105. Found: 319.122.

*3-(1H-benzo[d]imidazol-1-yl)-1-(4-methylphenyl)propan-1-one (**6b**)*. Yield: 19%. Mp: 109.0-110.0 ºC. IR (KBr) ν cm^{-1}: 1678 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.25 (s, 1H, **H$_{2'}$**); 7.86 (d, 2H, **H$_2$ + H$_6$**, $J_{2\text{-}3}$ = $J_{6\text{-}5}$ = 8.2 Hz); 7.68 (d, 1H, **H$_{8'}$**, $J_{8'\text{-}7'}$ = 7.8 Hz); 7.64 (d, 1H, **H$_{5'}$**, $J_{5'\text{-}6'}$ = 7.7 Hz); 7.30 (d, 2H, **H$_3$ + H$_5$**, $J_{3\text{-}2}$ = $J_{5\text{-}6}$ = 8.0 Hz); 7.25 (t, 1H, **H$_{7'}$**, $J_{7'\text{-}6'}$ = $J_{7'\text{-}8'}$ = 7.0 Hz); 7.19 (t, 1H, **H$_{6'}$**, $J_{6'\text{-}5'}$ = $J_{6'\text{-}7'}$ = 7.6 Hz); 4.60 (t, 2H, **CH$_2$-N**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 3.64 (t, 2H, **CH$_2$-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 2.35 (s, 3H, **CH$_3$**). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 197.74 (**CO**); 144.70 (**C$_{2'}$**); 144.35 (**C$_{4'}$**); 143.88 (**C$_4$**); 134.25 (**C$_1$**); 134.20 (**C$_{9'}$**); 129.73 (2C, **C$_3$+C$_5$**); 128.54 (2C, **C$_2$+C$_6$**); 122.70 (**C$_{7'}$**); 121.88 (**C$_{6'}$**); 119.83 (**C$_{5'}$**); 111.00 (**C$_{8'}$**); 39.93 (**CH$_2$-N**); 38.36 (**CH$_2$-CO**); 21.60 (**CH$_3$**). HRMS calculated for $C_{17}H_{16}N_2O$: 265.134. Found: 265.149.

*3-(1H-benzo[d]imidazol-1-yl)-1-(4-nitrophenyl)propan-1-one (**7b**)*. Yield: 22%. Mp: 153.0-154.0 ºC. IR (KBr) ν cm^{-1}: 1689 (s, $\nu_{C=O}$), 1521 (s, ν_{NO2}), 1348 (s, ν_{NO2}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.31 (d, 2H, **H$_3$ + H$_5$**, $J_{3\text{-}2}$ = $J_{5\text{-}6}$ = 8.9 Hz); 8.26 (s, 1H, **H$_{2'}$**); 8.19 (d, 2H, **H$_2$ + H$_6$**, $J_{2\text{-}3}$ = $J_{6\text{-}5}$ = 8.9 Hz); 7.70 (d, 1H, **H$_{8'}$**, $J_{8'\text{-}7'}$ = 7.9 Hz); 7.64 (d, 1H, **H$_{5'}$**, $J_{5'\text{-}6'}$ = 7.8 Hz); 7.26 (t, 1H, **H$_{7'}$**, $J_{7'\text{-}6'}$ = $J_{7'\text{-}8'}$ = 7.0 Hz); 7.20 (t, 1H, **H$_{6'}$**, $J_{6'\text{-}5'}$ = $J_{6'\text{-}7'}$ = 7.0 Hz); 4.63 (t, 2H, **CH$_2$-N**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 3.78 (t, 2H, **CH$_2$-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 197.07 (**CO**); 150.02 (**C$_4$**); 144.17 (**C$_{2'}$**); 143.40 (**C$_{4'}$**); 140.68 (**C$_1$**); 133.71 (**C$_{9'}$**); 129.40 (2C, **C$_2$+C$_6$**); 123.79 (2C, **C$_3$+C$_5$**); 122.23 (**C$_{7'}$**); 121.44 (**C$_{6'}$**); 119.36 (**C$_{5'}$**); 110.55 (**C$_{8'}$**); 39.22 (**CH$_2$-N**); 38.71 (**CH$_2$-CO**). HRMS calculated for $C_{16}H_{13}N_3O_3$: 296.103. Found: 296.121.

*3-(1H-benzo[d]imidazol-1-yl)-1-(thiophen-3-yl)propan-1-one (**8b**)*. Yield: 24%. Mp: 125.5-126.5 ºC. IR (KBr) ν cm^{-1}: 1674 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.51 (dd, 1H, **H$_2$**, $J_{2\text{-}4}$ = 1.7 Hz); 8.24 (s, 1H, **H$_{2'}$**); 7.67 (d, 1H, **H$_{8'}$**, $J_{8'\text{-}7'}$ = 7.9 Hz); 7.63 (d, 1H, **H$_{5'}$**, $J_{5'\text{-}6'}$ = 8.1 Hz); 7.61 (dd, 1H, **H$_5$**, $J_{5\text{-}4}$ = 5.3 Hz, $J_{5\text{-}2}$ = 3 Hz); 7.50 (d, 1H, **H$_4$**, $J_{4\text{-}5}$ = 5.0 Hz); 7.26 (t, 1H, **H$_{7'}$**, $J_{7'\text{-}6'}$ = $J_{7'\text{-}8'}$ = 7.3 Hz); 7.19 (t, 1H, **H$_{6'}$**, $J_{6'\text{-}5'}$ = $J_{6'\text{-}7'}$ = 7.4 Hz); 4.59 (t, 2H, **CH$_2$-N**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 3.58 (t, 2H, **CH$_2$-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 192.08 (**CO**); 144.18 (**C$_{2'}$**); 143.38 (**C$_{4'}$**); 141.46 (**C$_3$**); 134.11 (**C$_2$**); 133.67 (**C$_{9'}$**); 127.54 (**C$_5$**); 126.34 (**C$_4$**); 122.22 (**C$_{7'}$**); 121.40 (**C$_{6'}$**); 119.35 (**C$_{5'}$**); 110.50 (**C$_{8'}$**); 39.27 (**CH$_2$-N**); 39.04 (**CH$_2$-CO**). Anal. HRMS calculated for $C_{14}H_{12}N_2OS$: 257.092. Found: 257.090.

*3-(1H-benzo[d]imidazol-1-yl)-1-(thiophen-2-yl)propan-1-one (**9b**)*. Yield: 23%. Mp: 115.0-116.0 ºC. IR (KBr) ν cm^{-1}: 1666 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.23 (s, 1H, **H$_{2'}$**); 7.99 (dd, 1H, **H$_5$**, $J_{5\text{-}4}$ = 4.9 Hz, $J_{5\text{-}3}$ = 1.1 Hz); 7.95 (dd, 1H, **H$_3$**, $J_{3\text{-}4}$ = 3.8 Hz, $J_{3\text{-}5}$ = 1.1 Hz); 7.67 (d, 1H, **H$_{8'}$**, $J_{8'\text{-}7'}$ = 7.9 Hz); 7.63 (d, 1H, **H$_{5'}$**, $J_{5'\text{-}6'}$ = 7.9 Hz); 7.26 (td, 1H, **H$_{7'}$**, $J_{7'\text{-}6'}$ = $J_{7'\text{-}8'}$ = 7.8 Hz, $J_{7'\text{-}5'}$ = 1.1 Hz); 7.22-7.17 (m, 2H, **H$_{6'}$** + **H$_4$**); 4.60 (t, 2H, **CH$_2$-N**, $J_{CH2\text{-}CH2}$ = 6.8

Hz); 3.62 (t, 2H, **CH_2-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 190.75 (**CO**); 144.18 (**$C_{2'}$**); 143.36 (**C_2**); 143.25 (**$C_{4'}$**); 135.17 (**C_5**); 133.79 (**$C_{9'}$**); 133.66 (**C_3**); 128.76 (**C_4**); 122.28 (**$C_{7'}$**); 121.45 (**$C_{6'}$**); 119.36 (**$C_{5'}$**); 110.51 (**$C_{8'}$**); 39.38 (**CH_2-N**); 38.39 (**CH_2-CO**). HRMS calculated for $C_{14}H_{12}N_2OS$: 257.092. Found: 257.093.

*3-(1H-benzo[d]imidazol-1-yl)-1-(furan-2-yl)propan-1-one (**10b**)*. Yield: 25%. Mp: 86.5-87.5 ºC. IR (KBr) ν cm^{-1}: 1669.89 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.21 (s, 1H, **$H_{2'}$**); 7.97 (d, 1H, **H_5**, $J_{5\text{-}4}$ = 1.1 Hz); 7.66 (d, 1H, **$H_{8'}$**, $J_{8'\text{-}7'}$ = 7.9 Hz); 7.63 (d, 1H, **$H_{5'}$**, $J_{5'\text{-}6'}$ = 7.9 Hz); 7.47 (d, 1H, **H_3**, $J_{3\text{-}4}$ = 3.3 Hz); 7.26 (td, 1H, **$H_{7'}$**, $J_{7'\text{-}6'}$ = $J_{7'\text{-}8'}$ = 7.7 Hz, $J_{7'\text{-}5'}$ = 1.2 Hz); 7.19 (t, 1H, **$H_{6'}$**, $J_{6'\text{-}5'}$ = $J_{6'\text{-}7'}$ = 7.5 Hz); 6.68 (dd, 1H, **H_4**, $J_{4\text{-}3}$ = 3.6 Hz, $J_{4\text{-}5}$ = 1.7 Hz); 4.59 (t, 2H, **CH_2-N**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 3.46 (t, 2H, **CH_2-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 185.87 (**CO**); 151.52 (**C_2**); 147.98 (**C_5**); 144.15 (**$C_{2'}$**); 143.36 (**$C_{4'}$**); 133.61 (**$C_{9'}$**); 122.27 (**$C_{7'}$**); 121.44 (**$C_{6'}$**); 119.37 (**$C_{5'}$**); 118.93 (**C_3**); 112.53 (**C_4**); 110.45 (**$C_{8'}$**); 38.85 (**CH_2-N**); 37.72 (**CH_2-CO**). HRMS calculated for $C_{14}H_{12}N_2O_2$: 241.097. Found: 241.113.

*3-(1H-benzo[d]imidazol-1-yl)-1-(naphthalene-2-yl)propan-1-one (**11b**)*. Yield: 27%. Mp: 159.0-160.0 ºC. IR (KBr) ν cm^{-1}: 1685.13 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.68 (s, 1H, **H_1**); 8.31 (s, 1H, **$H_{2'}$**) 8.07 (d, 1H, **H_3**, $J_{3\text{-}4}$ = 7.9 Hz); 7.99-7.96 (m, 3H, **H_4 + H_6 + H_9**); 7.73 (d, 1H, **$H_{8'}$**, $J_{8'\text{-}7'}$ = 7.9 Hz); 7.67-7.58 (m, 3H, **H_7 + H_8 + $H_{5'}$**); 7.27 (t, 1H, **$H_{7'}$**, $J_{7'\text{-}6'}$ = $J_{7'\text{-}8'}$ = 7.1 Hz); 7.21 (t, 1H, **$H_{6'}$**, $J_{6'\text{-}5'}$ = $J_{6'\text{-}7'}$ = 7.0 Hz); 4.68 (t, 2H, **CH_2-N**, $J_{CH2\text{-}CH2}$ = 6.9 Hz); 3.83 (t, 2H, **CH_2-CO**, $J_{CH2\text{-}CH2}$ = 6.9 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 197.70; 144.27; 143.46; 135.14; 133.77; 133.46; 132.15; 130.19; 129.59; 128.74; 128.30; 127.65; 126.95; 123.29; 122.27; 121.46; 119.39; 110.60; 39.57; 38.19. HRMS calculated for $C_{20}H_{16}N_2O$: 301.134. Found: 301.153.

*1-(benzo[b]thiophen-3-yl)-3-(1H-benzo[d]imidazol-1-yl)propan-1-one (**12b**)*. Yield: 19%. Mp: 175.0-176.0 ºC. IR (KBr) ν cm^{-1}: 1663.89 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.98 (s, 1H, **H_2**); 8.62 (d, 1H, **H_8**, $J_{8\text{-}7}$ = 7.7 Hz); 8.28 (s, 1H, **$H_{2'}$**); 8.07 (d, 1H, **H_5**, $J_{5\text{-}6}$ = 7.8 Hz); 7.71 (d, 1H, **$H_{8'}$**, $J_{8'\text{-}7'}$ = 8.0 Hz); 7.64 (d, 2H, **$H_{5'}$**, $J_{5'\text{-}6'}$ = 7.9 Hz); 7.53-7.43 (m, 2H, **H_6 + H_7**); 7.28-7.18 (m, 2H, **$H_{6'}$ + $H_{7'}$**); 4.66 (t, 2H, **CH_2-N**, $J_{CH2\text{-}CH2}$ = 6.9 Hz); 3.72 (t, 2H, **CH_2-CO**, $J_{CH2\text{-}CH2}$ = 6.9 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 193.19 (**CO**); 144.20 (**$C_{2'}$**); 143.41 (**$C_{4'}$**); 140.21 (**C_2**); 139.33 (**C_3**); 136.07 (**C_4**); 133.76 (**C_9**); 133.72 (**$C_{9'}$**); 125.81 (**C_6**); 125.38 (**C_7**); 124.61 (**C_8**); 122.89 (**C_5**); 122.25 (**$C_{7'}$**); 121.43 (**$C_{6'}$**); 119.37 (**$C_{5'}$**); 110.54 (**$C_{8'}$**); 39.45 (**CH_2-N**); 39.39 (**CH_2-CO**). HRMS calculated for $C_{18}H_{14}N_2OS$: 307.108. Found: 307.107.

*1-(benzo[b]thiophen-2-yl)-3-(1H-benzo[d]imidazol-1-yl)propan-1-one (**13b**)*. Yield: 21%. Mp: 169.0-170.0 ºC. IR (KBr) ν cm^{-1}: 1665.26 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.38 (s, 1H, **H_3**); 8.26 (s, 1H, **$H_{2'}$**); 8.04 (d, 1H, **H_5**, $J_{5\text{-}6}$ = 8.1 Hz); 7.98 (d, 1H, **H_8**, $J_{8\text{-}7}$ = 7.9 Hz); 7.71 (d, 1H, **$H_{8'}$**, $J_{8'\text{-}7'}$ = 8.0 Hz); 7.64 (d, 1H, **$H_{5'}$**, $J_{5'\text{-}6'}$ = 7.9 Hz); 7.53 (t, 1H, **H_6**, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.0 Hz); 7.46 (t, 1H, **H_7**, $J_{7\text{-}8}$ = $J_{7\text{-}6}$ =7.1 Hz); 7.27 (t, 1H, **$H_{7'}$**, $J_{7'\text{-}6'}$ = $J_{7'\text{-}8'}$ = 7.2 Hz); 7.20 (t, 1H, **$H_{6'}$**, $J_{6'\text{-}5'}$ = $J_{6'\text{-}7'}$ = 7.1 Hz); 4.65 (t, 2H, **CH_2-N**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 3.75 (t, 2H, **CH_2-CO**, $J_{CH2\text{-}}$

$_{CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 192.54 (**CO**); 144.22 (**C$_{2'}$**); 143.40 (**C$_{4'}$**); 142.54 (**C$_2$**); 141.50 (**C$_4$**); 139.06 (**C$_9$**); 133.68 (**C$_{9'}$**); 131.31 (**C$_3$**); 127.85 (**C$_6$**); 126.35 (**C$_8$**); 125.31 (**C$_7$**); 123.17 (**C$_5$**); 122.31 (**C$_7$**); 121.49 (**C$_{6'}$**); 119.39 (**C$_{5'}$**); 110.58 (**C$_{8'}$**); 39.41 (**CH$_2$-N**); 38.41 (**CH$_2$-CO**). HRMS calculated for $C_{18}H_{14}N_2OS$: 307.108. Found: 307.196.

*3-(1H-imidazol-1-yl)-1-(benzofuran-2-yl)propan-1-one (**14b**)*. Yield: 21%. Mp: 157.0-158.0 ºC. IR (KBr) ν cm^{-1}: 1680.14 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.26 (s, 1H, **H$_{2'}$**); 7.93 (s, 1H, **H$_3$**); 7.81 (d, 1H, **H$_5$**, $J_{5\text{-}6}$ = 7.8 Hz); 7.73-7.67 (m, 2H, **H$_8$ + H$_{8'}$**); 7.64 (d, 1H, **H$_{5'}$**, $J_{5'\text{-}6'}$ = 8.0 Hz); 7.54 (ddd, 1H, **H$_7$**, $J_{7\text{-}8}$ = 8.4 Hz, $J_{7\text{-}6}$ = 7.3 Hz, $J_{7\text{-}5}$ = 1.2 Hz); 7.36 (t, 1H, **H$_6$**, $J_{6\text{-}5}$ = $J_{6\text{-}7}$ = 7.2 Hz); 7.28 (t, 1H, **H$_{7'}$**, $J_{7'\text{-}6'}$ = $J_{7'\text{-}8'}$ = 7.1 Hz); 7.20 (t, 1H, **H$_{6'}$**, $J_{6'\text{-}5'}$ = $J_{6'\text{-}7'}$ = 7.0 Hz); 4.66 (t, 2H, **CH$_2$-N**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 3.64 (t, 2H, **CH$_2$-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 188.11 (**CO**); 154.97 (**C$_9$**); 151.61 (**C$_2$**); 144.20 (**C$_{2'}$**); 143.40 (**C$_{4'}$**); 133.66 (**C$_{9'}$**); 128.65 (**C$_7$**); 126.69 (**C$_4$**); 124.11 (**C$_6$**); 123.74 (**C$_5$**); 122.32 (**C$_{7'}$**); 121.50 (**C$_{6'}$**); 119.41 (**C$_{5'}$**); 114.50 (**C$_3$**); 112.26 (**C$_8$**); 110.54 (**C$_{8'}$**); 38.88 (**CH$_2$-N**); 38.26 (**CH$_2$-CO**). HRMS calculated for $C_{18}H_{14}N_2O_2$: 291.113. Found: 291.131.

*3-(1H-benzo[d]imidazol-1-yl)-1-(3,5-dimethoxyphenyl)propan-1-one (**15b**)*. Yield: 24%. Mp: 160.0-161.0 ºC. IR (KBr) ν cm^{-1}: 1685.35 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.25 (s, 1H, **H$_{2'}$**); 7.68 (d, 1H, **H$_{8'}$**, $J_{8'\text{-}7'}$ = 7.9 Hz); 7.63 (d, 1H, **H$_{5'}$**, $J_{5'\text{-}6'}$ = 7.9 Hz); 7.26 (t, 1H, **H$_{7'}$**, $J_{7'\text{-}6'}$ = $J_{7'\text{-}8'}$ = 7.0 Hz); 7.19 (t, 1H, **H$_{6'}$**, $J_{6'\text{-}5'}$ = $J_{6'\text{-}7'}$ = 7.0 Hz); 7.07 (d, 2H, **H$_2$ + H$_6$**, $J_{2\text{-}4}$ = $J_{6\text{-}4}$ = 2.3 Hz); 6.75 (t, 1H, **H$_4$**, $J_{4\text{-}2}$ = $J_{4\text{-}6}$ = 2.2 Hz); 4.59 (t, 2H, **CH$_2$-N**, $J_{CH2\text{-}CH2}$ = 6.7 Hz); 3.77 (s, 6H, **OCH$_3$**); 3.67 (t, 2H, **CH$_2$-CO**, $J_{CH2\text{-}CH2}$ = 6.7 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 197.54 (**CO**); 160.59 (2C, **C$_3$+C$_5$**); 144.25 (**C$_{2'}$**); 143.38 (**C$_{4'}$**); 138.25 (**C$_1$**); 133.75 (**C$_{9'}$**); 122.24 (**C$_{7'}$**); 121.43 (**C$_{6'}$**); 119.35 (**C$_{5'}$**); 110.58 (**C$_{8'}$**); 105.67 (2C, **C$_2$+C$_6$**); 105.42 (**C$_4$**); 55.52 (2C, **OCH$_3$**); 39.45 (**CH$_2$-N**); 38.22 (**CH$_2$-CO**). HRMS calculated for $C_{18}H_{18}N_2O_3$: 311.139. Found: 311.159.

*1-(3-benzo[d][1,3]dioxol-5-yl)-3-(1H-benzo[d]imidazol-1-yl)propan-1-one (**16b**)*. Yield: 22%. Mp: 132.5-133.5 ºC. IR (KBr) ν cm^{-1}: 1675.26 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.24 (s, 1H, **H$_{2'}$**); 7.68-7.59 (m, 3H, **H$_7$ + H$_{5'}$ + H$_{8'}$**); 7.45 (d, 1H, **H$_2$**, $J_{2\text{-}7}$ = 1.6 Hz); 7.25 (t, 1H, **H$_{7'}$**, $J_{7'\text{-}6'}$ = $J_{7'\text{-}8'}$ = 7.1 Hz); 7.19 (t, 1H, **H$_{6'}$**, $J_{6'\text{-}5'}$ = $J_{6'\text{-}7'}$ = 7.0 Hz); 7.00 (d, 1H, **H$_6$**, $J_{6\text{-}7}$ = 8.2 Hz); 6.12 (s, 2H, **H$_4$**); 4.58 (t, 2H, **CH$_2$-N**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 3.60 (t, 2H, **CH$_2$-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 195.75 (**CO**); 151.66 (**C$_5$**); 147.84 (**C$_3$**); 144.23 (**C$_{2'}$**); 143.39 (**C$_{4'}$**); 133.73 (**C$_{9'}$**); 130.91 (**C$_1$**); 124.53 (**C$_7$**); 122.23 (**C$_{7'}$**); 121.42 (**C$_{6'}$**); 119.35 (**C$_{5'}$**); 110.55 (**C$_{8'}$**); 108.06 (**C$_6$**); 107.33 (**C$_2$**); 102.07 (**C$_4$**); 39.29 (**CH$_2$-N**); 37.76 (**CH$_2$-CO**). HRMS calculated for $C_{17}H_{14}N_2O_3$: 295.108. Found: 295.126.

*1-(adamantan-1-yl)-3-(1H-benzo[d]imidazol-1-yl)propan-1-one (**17b**)*. Yield: 20%. Mp: 114.5-115.5 ºC. IR (KBr) ν cm^{-1}: 1695 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.15 (s, 1H, **H$_{2'}$**); 7.63-7.60 (m, 2H, **H$_{5'}$ + H$_{8'}$**); 7.25 (t, 1H, **H$_{7'}$**, $J_{7'\text{-}6'}$ = $J_{7'\text{-}8'}$ = 7.2 Hz); 7.18 (t, 1H, **H$_{6'}$**, $J_{6'\text{-}5'}$ = $J_{6'\text{-}7'}$ = 7.1 Hz); 4.41 (t, 2H, **CH$_2$-N**, $J_{CH2\text{-}CH2}$ = 6.7 Hz); 3.10 (t, 2H, **CH$_2$-CO**, $J_{CH2\text{-}}$

J_{CH2} = 6.7 Hz); 1.92 (s, 3H, **H_3 + H_5 + H_8**); 1.68-1.56 (m, 12H, **H_2 + H_4 + H_6 + H_7 + H_9 + H_{10}**). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 213.18 (**CO**); 144.59 (**$C_{2'}$**); 143.81 (**$C_{4'}$**); 134.11 (**$C_{9'}$**); 122.67 (**$C_{7'}$**); 121.83 (**$C_{6'}$**); 119.82 (**$C_{5'}$**); 110.91 (**$C_{8'}$**); 46.02 (**C_1**); 39.72 (**CH_2-N**); 37.64 (3C, **C_2+C_6+C_7**); 36.37 (3C, **C_4+C_9+C_{10}**); 36.11 (**CH_2-CO**); 27.71 (3C, **C_3+C_5+C_8**). HRMS calculated for $C_{20}H_{24}N_2O$: 309.196. Found: 309.215.

1-(4-fluorophenyl)-3-(2-nitro-1H-imidazol-1-yl)propan-1-one (**1c**). Yield: 21%. Mp: 92.5-93.5 ºC. IR (KBr) ν cm^{-1}: 1679 (s, $\nu_{C=O}$), 1532 (s, ν_{NO2}), 1362 (s, ν_{NO2}), 1216 (s, ν_{C-F}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.05 (dd, 2H, **H_2 + H_6**, J_{2-3} = J_{6-5} = 8.9 Hz, J_{2-F} = J_{6-F} = 5.5 Hz); 7.70 (d, 1H, **$H_{5'}$**, $J_{5'-4'}$ = 0.9 Hz); 7.35 (t, 2H, **H_3 + H_5**, J_{3-2} = J_{5-6} = 8.9 Hz); 7.16 (d, 1H, **$H_{4'}$**, $J_{4'-5'}$ = 0.9 Hz); 4.74 (t, 2H, **CH_2-N**, $J_{CH2-CH2}$ = 6.8 Hz); 3.70 (t, 2H, **CH_2-CO**, $J_{CH2-CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 196.09; 165.21 (d, ^1J = 252.1 Hz); 144.85; 132.79 (d, ^4J = 2.8 Hz); 131.04 (2C, d, ^3J = 9.5 Hz); 127.99; 127.61; 115.75 (2C, d, ^2J = 21.9 Hz); 44.59; 39.49. Anal. Calc. for $C_{12}H_{10}FN_3O_3$: C 54.76%, H 3.83%, N 15.96%. Found: C 54.72%, H 3.93%, N 15.69%.

1-(4-chlorophenyl)-3-(2-nitro-1H-imidazol-1-yl)propan-1-one (**2c**) Yield: 23%. Mp: 113.5-114.5 ºC. IR (KBr) ν cm^{-1}: 1680 (s, $\nu_{C=O}$), 1540 (s, ν_{NO2}), 1352 (s, ν_{NO2}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 7.98 (d, 2H, **H_2 + H_6**, J_{2-3} = J_{6-5} = 8.6 Hz); 7.70 (d, 1H, **$H_{5'}$**, $J_{5'-4'}$ = 0.9 Hz); 7.60 (d, 2H, **H_3 + H_5**, J_{3-2} = J_{5-6} = 8.6 Hz); 7.16 (d, 1H, **$H_{4'}$**, $J_{4'-5'}$ = 0.9 Hz); 4.74 (t, 2H, **CH_2-N**, $J_{CH2-CH2}$ = 6.7 Hz); 3.70 (t, 2H, **CH_2-CO**, $J_{CH2-CH2}$ = 6.7 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 196.55; 144.86; 138.47; 134.70; 130.45; 129.92 (2C); 129.00; 128.85 (2C); 128.00; 127.61; 44.54; 38.55. Anal. Calc. for $C_{12}H_{10}ClN_3O_3$: C 51.53%, H 3.60%, N 15.02%. Found: C 51.55%, H 3.69%, N 14.91%.

1-(4-methoxyphenyl)-3-(2-nitro-1H-imidazol-1-yl)propan-1-one (**3c**) Yield: 16%. Mp: 140.5-141.5 ºC. IR (KBr) ν cm^{-1}: 1665 (s, $\nu_{C=O}$), 1532 (s, ν_{NO2}), 1354 (s, ν_{NO2}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 7.95 (d, 2H, **H_2 + H_6**, J_{2-3} = J_{6-5} = 8.9 Hz); 7.70 (s, 1H, **$H_{5'}$**); 7.16 (s, 1H, **$H_{4'}$**); 7.04 (d, 2H, **H_3 + H_5**, J_{3-2} = J_{5-6} = 8.9 Hz); 4.73 (t, 2H, **CH_2-N**, $J_{CH2-CH2}$ = 6.8 Hz); 3.84 (s, 3H, **OCH_3**); 3.63 (t, 2H, **CH_2-CO**, $J_{CH2-CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 195.75; 163.41; 130.34 (2C); 129.01; 127.95; 127.62; 113.92 (2C); 55.57; 44.77; 38.16. Anal. Calc. for $C_{13}H_{13}N_3O_4$: C 56.72%, H 4.76%, N 15.27%. Found: C 56.55%, H 4.74%, N 15.72%.

1-(benzo[b]thiophen-3-yl)-3-(2-nitro-1H-imidazol-1-yl)propan-1-one (**4c**). Yield: 23%. Mp: 138.0-139.0 ºC. IR (KBr) ν cm^{-1}: 1663 (s, $\nu_{C=O}$), 1532 (s, ν_{NO2}), 1351 (s, ν_{NO2}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.99 (s, 1H, **H_2**); 8.59 (dt, 1H, **H_5**, J_{5-6} = 8.2 Hz, J_{5-8} = 0.9 Hz); 8.09 (dt, 1H, **H_8**, J_{8-7} = 7.8 Hz, J_{8-5} = 0.9 Hz); 7.73 (d, 1H, **$H_{5'}$**, $J_{5'-4'}$ = 1.1 Hz); 7.54-7.17 (m, 2H, **H_6+H_7**); 7.17 (d, 1H, **$H_{4'}$**, $J_{4'-5'}$ = 1.0 Hz); 4.79 (t, 2H, **CH_2-N**, $J_{CH2-CH2}$ = 6.8 Hz); 3.73 (t, 2H, **CH_2-CO**, $J_{CH2-CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 192.82; 140.45; 139.37;

136.06; 133.58; 128.09; 127.71; 125.89; 125.46; 124.59; 122.98; 44.71; 39.82. Anal. Calc. for $C_{14}H_{11}N_3O_3S$: C 55.81%, H 3.68%, N 13.95%. Found: C 55.59%, H 3.93%, N 13.86%.

1-(4-fluorophenyl)-3-(2-methyl-1H-imidazol-1-yl)propan-1-one (**1d**). Yield: 21%. Mp: 117.0-117.5 ºC. IR (KBr) ν cm^{-1}: 1673 (s, $\nu_{C=O}$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.95-7.91 (m, 2H, **H_2 + H_6**); 7.13 (t, 2H, **H_3 + H_5**, $J_{3-2} = J_{5-6} = 8.6$ Hz); 6.87 (dd, 2H, **$H_{4'}$ + $H_{5'}$**, $J_{4'-5'} = J_{5'-4'} = 6.0$ Hz, $J_{4'-CH3} = J_{5'-CH3} = 1.2$ Hz); 4.30 (t, 2H, **CH_2-N**, $J_{CH2-CH2} = 6.8$ Hz); 3.35 (t, 2H, **CH_2-CO**, $J_{CH2-CH2} = 6.8$ Hz); 2.42 (s, 3H, **CH_3-Amine**). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 195.18; 166.18 (d, $^1J = 255.8$ Hz); 144.60; 132.75 (d, $^4J = 2.9$ Hz); 130.76 (2C, d, $^3J = 9.4$ Hz); 127.70; 119.18; 116.09 (2C, d, $^2J = 21.8$ Hz); 40.70; 39.33; 13.20. Anal. Calc. for $C_{13}H_{13}FN_2O$: C 67.23%, H 5.64%, N 12.06%. Found: C 67.58%, H 5.94%, N 12.09%.

1-(4-chlorophenyl)-3-(2-methyl-1H-imidazol-1-yl)propan-1-one (**2d**) Yield: 14%. Mp: 144.0-145.0 ºC. IR (KBr) ν cm^{-1}: 1674 (s, $\nu_{C=O}$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.84 (d, 2H, **H_2 + H_6**, $J_{2-3} = J_{6-5} = 8.6$ Hz); 7.44 (d, 2H, **H_3 + H_5**, $J_{3-2} = J_{5-6} = 8.6$ Hz); 6.88 (d, 2H, **$H_{4'}$ + $H_{5'}$**, $J_{4'-5'} = J_{5'-4'} = 7.0$ Hz); 4.31 (t, 2H, **CH_2-N**, $J_{CH2-CH2} = 6.8$ Hz); 3.35 (t, 2H, **CH_2-CO**, $J_{CH2-CH2} = 6.8$ Hz); 2.42 (s, 3H, **CH_3-Amine**). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 195.60; 144.62; 140.42; 134.60; 129.49 (2C); 129.29 (2C); 127.75; 119.18; 40.67; 39.42; 13.22. Anal. Calc. for $C_{13}H_{13}ClN_2O$: C 62.78%, H 5.27%, N 11.26%. Found: C 62.55%, H 5.41%, N 11.22%.

1-(4-methoxyphenyl)-3-(2-methyl-1H-imidazol-1-yl)propan-1-one (**3d**) Yield: 20%. Mp: 104.0-105.0 ºC. IR (KBr) ν cm^{-1}: 1666 (s, $\nu_{C=O}$). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 7.95 (d, 2H, **H_2 + H_6**, $J_{2-3} = J_{6-5} = 9.0$ Hz); 7.07 (d, 1H, **$H_{5'}$**, $J_{5'-CH3} = 1.3$ Hz); 7.03 (d, 2H, **H_3 + H_5**, $J_{3-2} = J_{5-6} = 8.9$ Hz); 6.68 (d, 1H, **$H_{4'}$**, $J_{4'-CH3} = 1.3$ Hz); 4.19 (t, 2H, **CH_2-N**, $J_{CH2-CH2} = 6.9$ Hz); 3.84 (s, 3H, **OCH_3**); 3.46 (t, 2H, **CH_2-CO**, $J_{CH2-CH2} = 6.9$ Hz); 2.31 (s, 3H, **CH_3-Amine**). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 196.07; 163.32; 143.84; 130.34 (2C); 129.28; 126.27; 119.38; 113.91 (2C); 55.57; 40.47; 38.52; 12.64. Anal. Calc. for $C_{14}H_{16}N_2O_2$: C 68.83%, H 6.60%, N 11.47%. Found: C 68.73%, H 6.49%, N 11.86%.

1-(benzo[b]thiophen-3-yl)-3-(2-methyl-1H-imidazol-1-yl)propan-1-one (**4d**). Yield: 16%. Mp: 113.0-114.0 ºC. IR (KBr) ν cm^{-1}: 1655 (s, $\nu_{C=O}$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 8.74 (d, 1H, **H_5**, $J_{5-6} = 8.2$ Hz); 8.21 (s, 1H, **H_2**); 7.87 (d, 1H, **H_8**, $J_{8-7} = 8.0$ Hz); 7.51 (t, 1H, **H_6**, $J_{6-7} = 7.6$ Hz); 7.44 (t, 1H, **H_7**, $J_{7-6} = 7.6$ Hz); 6.90 (d, 2H, **$H_{4'}$ + $H_{5'}$**, $J_{4'-CH3} = J_{5'-CH3} = 1.6$ Hz); 4.36 (t, 2H, **CH_2-N**, $J_{CH2-CH2} = 6.8$ Hz); 3.41 (t, 2H, **CH_2-CO**, $J_{CH2-CH2} = 6.8$ Hz); 2.44 (s, 3H, **CH_3-Amine**). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 191.73; 144.64; 139.92; 137.43; 136.39; 134.78; 127.73; 126.22; 125.87; 125.63; 122.47; 119.22; 40.85; 40.82; 13.23. Anal. Calc. for $C_{15}H_{14}N_2OS$: C 66.64%, H 5.22%, N 10.36%. Found: C 67.04%, H 5.34%, N 10.32%.

1-(4-fluorophenyl)-3-(4-nitro-1H-imidazol-1-yl)propan-1-one (**1e**). Yield: 22%. Mp: 137.5-138.5 ºC. IR (KBr) ν cm^{-1}: 1684 (s, $\nu_{C=O}$), 1520 (s, ν_{NO2}), 1335 (s, ν_{NO2}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.46 (d, 1H, **$H_{5'}$**, $J_{5'-2'} = 1.5$ Hz); 8.07 (dd, 2H, **H_2 + H_6**, $J_{2-3} = J_{6-5} = 8.8$ Hz, $J_{2-F} = J_{6-F} = 5.6$ Hz); 7.91 (d, 1H, **$H_{2'}$**, $J_{2'-5'} = 1.4$ Hz); 7.37 (t, 2H, **H_3 + H_5**, $J_{3-2} = J_{5-6} = 8.8$

Hz); 4.43 (t, 2H, **CH_2-N**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 3.73 (t, 2H, **CH_2-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 195.99; 165.24 (d, ^1J = 252.2 Hz); 163.99; 146.84; 137.71; 132.80 (d, ^4J = 3.2 Hz); 131.04 (2C, d, ^3J = 9.5 Hz); 121.75; 115.79 (2C, d, ^2J = 21.9 Hz); 42.64; 38.44. Anal. Calc. for $C_{12}H_{10}FN_3O_3$: C 54.76%, H 3.83%, N 15.96%. Found: C 54.98%, H 3.85%, N 15.82%.

1-(4-chlorophenyl)-3-(4-nitro-1H-imidazol-1-yl)propan-1-one (**2e**) Yield: 26%. Mp: 147.0-148.0 ºC. IR (KBr) ν cm^{-1}: 1670 (s, $\nu_{C=O}$), 1525 (s, ν_{NO2}), 1336 (s, ν_{NO2}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.46 (d, 1H, **$H_{5'}$**, $J_{5'\text{-}2'}$ = 1.5 Hz); 8.00 (d, 1H, **H_2 + H_6**, $J_{2\text{-}3}$ = $J_{6\text{-}5}$ = 8.6 Hz); 7.92 (d, 1H, **$H_{2'}$**, $J_{2'\text{-}5'}$ = 1.4 Hz); 7.62 (d, 2H, **H_3 + H_5**, $J_{3\text{-}2}$ = $J_{5\text{-}6}$ = 8.5 Hz); 4.43 (t, 2H, **CH_2-N**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 3.74 (t, 2H, **CH_2-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 196.43; 146.84; 138.52; 137.70; 134.69; 129.91 (2C); 128.89 (2C); 121.74; 42.58; 38.51. Anal. Calc. for $C_{12}H_{10}ClN_3O_3$: C 51.53%, H 3.60%, N 15.02%. Found: C 51.37%, H 3.51%, N 15.18%.

1-(4-methoxyphenyl)-3-(4-nitro-1H-imidazol-1-yl)propan-1-one (**3e**) Yield: 17%. Mp: 156.5-157.5 ºC. IR (KBr) ν cm^{-1}: 1676 (s, $\nu_{C=O}$), 1518 (s, ν_{NO2}), 1330 (s, ν_{NO2}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.46 (d, 1H, **$H_{5'}$**, $J_{5'\text{-}2'}$ = 1.5 Hz); 7.96 (d, 2H, **H_2 + H_6**, $J_{2\text{-}3}$ = $J_{6\text{-}5}$ = 9.0 Hz); 7.91 (d, 1H, **$H_{2'}$**, $J_{2'\text{-}5'}$ = 1.5k Hz); 7.05 (d, 2H, **H_3 + H_5**, $J_{3\text{-}2}$ = $J_{5\text{-}6}$ = 8.9 Hz); 4.41 (t, 2H, **CH_2-N**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 3.84 (s, 3H, **OCH_3**); 3.67 (t, 2H, **CH_2-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 195.65; 163.44; 146.83; 137.71; 130.34 (2C); 129.02; 121.76; 113.95 (2C); 55.58; 42.82; 38.11. Anal. Calc. for $C_{13}H_{13}N_3O_4$: C 56.72%, H 4.76%, N 15.27%. Found: C 56.55%, H 4.74%, N 15.72%.

1-(benzo[b]thiophen-3-yl)-3-(4-nitro-1H-imidazol-1-yl)propan-1-one (**4e**). Yield: 21%. Mp: 209.5-210.5 ºC. IR (KBr) ν cm^{-1}: 1664 (s, $\nu_{C=O}$), 1521 (s, ν_{NO2}), 1324 (s, ν_{NO2}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 9.02 (s, 1H, **H_2**); 8.59 (dd, 1H, **H_5**, $J_{5\text{-}6}$ = 7.7 Hz, $J_{5\text{-}8}$ = 1.3 Hz); 8.49 (d, 1H, **$H_{5'}$**, $J_{5'\text{-}2'}$ = 1.4 Hz); 8.10 (d, 1H, **H_8**, $J_{8\text{-}7}$ = 7.4 Hz); 7.94 (d, 1H, **$H_{2'}$**, $J_{2'\text{-}4'}$ = 1.4 Hz); 7.54-7.45 (m, 2H, **H_6+H_7**); 4.48 (t, 2H, **CH_2-N**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 3.76 (t, 2H, **CH_2-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 192.76; 140.48; 139.37; 137.75; 136.02; 133.60; 125.91; 125.48; 124.57; 122.99; 121.78; 42.74; 39.84. Anal. Calc. for $C_{14}H_{11}N_3O_3S$: C 55.81%, H 3.68%, N 13.95%. Found: C 56.03%, H 3.57%, N 14.15%.

1-(4-fluorophenyl)-3-(2-methyl-5-nitro-1H-imidazol-1-yl)propan-1-one (**1f**). Yield: 16%. Mp: 197.0-198.0 ºC. IR (KBr) ν cm^{-1}: 1684 (s, $\nu_{C=O}$), 1527 (s, ν_{NO2}), 1388 (s, ν_{NO2}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.36 (s, 1H, **$H_{4'}$**); 8.08 (dd, 2H, **H_2 + H_6**, $J_{2\text{-}3}$ = $J_{6\text{-}5}$ = 8.5 Hz, $J_{2\text{-}F}$ = $J_{6\text{-}F}$ = 5.6 Hz); 7.37 (t, 2H, **H_3 + H_5**, $J_{3\text{-}2}$ = $J_{5\text{-}6}$ = 8.8 Hz); 4.32 (t, 2H, **CH_2-N**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 3.69 (t, 2H, **CH_2-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 2.43 (s, 3H, **CH_3-Amine**). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 196.01; 165.24 (d, ^1J = 251.7 Hz); 145.36; 132.83 (d, ^4J = 2.9 Hz); 131.09 (2C, d, ^3J = 9.7 Hz); 122.13 (2C); 115.78 (2C, d, ^2J = 21.8 Hz); 41.62; 38.13; 12.69. Anal. Calc. for $C_{13}H_{12}FN_3O_3$: C 56.32%, H 4.36%, N 15.16%. Found: C 56.39%, H 4.48%, N 15.18%.

1-(4-chlorophenyl)-3-(2-methyl-5-nitro-1H-imidazol-1-yl)propan-1-one (**2f**) Yield: 13%. Mp: 194.5-195.5 ºC. IR (KBr) ν cm^{-1}: 1686 (s, $\nu_{C=O}$), 1568 (s, ν_{NO2}), 1387 (s, ν_{NO2}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.35 (s, 1H, **$H_{4'}$**); 8.01 (d, 2H, **H_2 + H_6**, $J_{2-3} = J_{6-5} = 8.0$ Hz); 7.61 (d, 2H, **H_3 + H_5**, $J_{3-2} = J_{5-6} = 8.2$ Hz); 4.32 (t, 2H, **CH_2-N**, $J_{CH2-CH2} = 6.8$ Hz); 3.69 (t, 2H, **CH_2-CO**, $J_{CH2-CH2} = 6.8$ Hz); 2.43 (s, 3H, **CH_3-Amine**). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 196.45; 145.34; 138.50; 134.73; 129.96 (2C); 128.86 (2C); 122.13; 41.56; 38.22; 12.68. Anal. Calc. for $C_{13}H_{12}ClN_3O_3$: C 53.16%, H 4.12%, N 14.31%. Found: C 53.16%, H 4.12%, N 14.31%.

1-(4-methoxyphenyl)-3-(2-methyl-5-nitro-1H-imidazol-1-yl)propan-1-one (**3f**) Yield: 23%. Mp: 139.5-140.5 ºC. IR (KBr) ν cm^{-1}: 1678 (s, $\nu_{C=O}$), 1572 (s, ν_{NO2}), 1391 (s, ν_{NO2}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.36 (s, 1H, **$H_{4'}$**); 7.97 (d, 2H, **H_2 + H_6**, $J_{2-3} = J_{6-5} = 8.9$ Hz); 7.05 (d, 2H, **H_3 + H_5**, $J_{3-2} = J_{5-6} = 8.9$ Hz); 4.30 (t, 2H, **CH_2-N**, $J_{CH2-CH2} = 6.8$ Hz); 3.84 (s, 3H, **OCH_3**); 3.62 (t, 2H, **CH_2-CO**, $J_{CH2-CH2} = 6.8$ Hz); 2.43 (s, 3H, **CH_3-Amine**). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 195.69; 163.43; 145.34; 130.40 (2C); 129.05; 122.12; 113.93 (2C); 55.59; 41.79; 37.77; 12.69. Anal. Calc. for $C_{14}H_{15}N_3O_4$: C 58.13%, H 5.23%, N 14.53%. Found: C 58.30%, H 5.41%, N 14.70%.

1-(benzo[b]thiophen-3-yl)-3-(2-methyl-5-nitro-1H-imidazol-1-yl)propan-1-one (**4d**). Yield: 21%. Mp: 113.0-114.0 ºC. IR (KBr) ν cm^{-1}: 1666 (s, $\nu_{C=O}$), 1528 (s, ν_{NO2}), 1392 (s, ν_{NO2}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 9.03 (s, 1H, **H_2**); 8.60 (d, 1H, **H_5**, $J_{5-6} = 7.9$ Hz); 8.39 (s, 1H, **$H_{4'}$**); 8.09 (d, 1H, **H_8**, $J_{8-7} = 7.8$ Hz); 7.49 (dt, 1H, **H_6 + H_7**, $J_{6-5} = J_{7-8} = 21.5$, Hz $J_{6-7} = J_{7-6} = 7.1$ Hz); 4.37 (t, 2H, **CH_2-N**, $J_{CH2-CH2} = 6.9$ Hz); 3.72 (t, 2H, **CH_2-CO**, $J_{CH2-CH2} = 6.9$ Hz); 2.45 (s, 3H, **CH_3-Amine**). ^{13}C NMR (DMSO-d_{6j}, 100 MHz) δ ppm: 192.76; 145.36; 145.33; 140.46; 139.34; 136.02; 133.62; 125.89; 125.45; 124.56; 122.97; 122.11; 41.71; 39.45; 12.69. Anal. Calc. for $C_{15}H_{13}N_3O_3S$: C 57.13%, H 4.16%, N 13.33%. Found: C 57.26%, H 4.02%, N 10.32%.

1-(4-fluorophenyl)-3-(5-methyl-4-nitro-1H-imidazol-1-yl)propan-1-one (**1g**). Yield: 16%. Mp: 140.5-141.5 ºC. IR (KBr) ν cm^{-1}: 1678 (s, $\nu_{C=O}$), 1535 (s, ν_{NO2}), 1353 (s, ν_{NO2}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.08 (dd, 2H, **H_2 + H_6**, $J_{2-3} = J_{6-5} = 8.2$ Hz, $J_{2-F} = J_{6-F} = 5.7$ Hz); 7.82 (s, 1H, **$H_{2'}$**); 7.37 (t, 2H, **H_3 + H_5**, $J_{3-2} = J_{5-6} = 8.8$ Hz); 4.37 (t, 2H, **CH_2-N**, $J_{CH2-CH2} = 6.7$ Hz); 3.64 (t, 2H, **CH_2-CO**, $J_{CH2-CH2} = 6.8$ Hz); 2.63 (s, 3H, **CH_3-Amine**). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 195.93; 165.22 (d, $^1J = 252.2$ Hz); 143.78; 135.93; 132.82 (d, $^4J = 2.9$ Hz); 131.94; 131.07 (2C, d, $^3J = 9.5$ Hz); 115.76 (2C, d, $^2J = 21.8$ Hz); 40.26; 38.04; 10.16. Anal. Calc. for $C_{13}H_{12}FN_3O_3$: C 56.32%, H 4.36%, N 15.16%. Found: C 56.31%, H 4.30%, N 15.22%.

1-(4-chlorophenyl)-3-(5-methyl-4-nitro-1H-imidazol-1-yl)propan-1-one (**2g**) Yield: 15%. Mp: 164.5-165.5 ºC. IR (KBr) ν cm^{-1}: 1686 (s, $\nu_{C=O}$), 1566 (s, ν_{NO2}), 1342 (s, ν_{NO2}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 7.99 (d, 2H, **H_2 + H_6**, $J_{2-3} = J_{6-5} = 8.6$ Hz); 7.81 (s, 1H, **$H_{2'}$**); 7.61 (d, 2H, **H_3 + H_5**, $J_{3-2} = J_{5-6} = 8.6$ Hz); 4.36 (t, 2H, **CH_2-N**, $J_{CH2-CH2} = 6.8$ Hz); 3.64 (t, 2H,

CH_2-CO, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 2.63 (s, 3H, **CH_3-Amine**). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 196.37; 143.78; 138.48; 135.93; 134.72; 131.94; 129.95 (2C); 128.84 (2C); 40.21; 38.12; 10.16. Anal. Calc. for $C_{13}H_{12}ClN_3O_3$: C 53.16%, H 4.12%, N 14.31%. Found: C 53.14%, H 4.27%, N 14.26%.

1-(4-methoxyphenyl)-3-(5-methyl-4-nitro-1H-imidazol-1-yl)propan-1-one (**3g**) Yield: 27%. Mp: 149.0-150.0 ºC. IR (KBr) ν cm^{-1}: 1682 (s, $\nu_{C=O}$), 1565 (s, ν_{NO2}), 1403 (s, ν_{NO2}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 7.97 (d, 2H, **H_2 + H_6**, $J_{2\text{-}3} = J_{6\text{-}5}$ = 8.9 Hz); 7.82 (s, 1H, **$H_{2'}$**); 7.05 (d, 2H, **H_3 + H_5**, $J_{3\text{-}2} = J_{5\text{-}6}$ = 8.9 Hz); 4.35 (t, 2H, **CH_2-N**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 3.85 (s, 3H, **OCH_3**); 3.58 (t, 2H, **CH_2-CO**, $J_{CH2\text{-}CH2}$ = 6.8 Hz); 2.64 (s, 3H, **CH_3-Amine**). ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 195.60; 163.42; 143.76; 135.93; 131.92; 130.38 (2C); 129.03; 113.92 (2C); 55.59; 40.42; 37.68; 10.16. Anal. Calc. for $C_{14}H_{15}N_3O_4$: C 58.13%, H 5.23%, N 14.53%. Found: C 58.44%, H 5.40%, N 14.49%.

1-(benzo[b]thiophen-3-yl)-3-(5-methyl-4-nitro-1H-imidazol-1-yl)propan-1-one (**4g**). Yield: 16%. Mp: 180.0-181.0 ºC. IR (KBr) ν cm^{-1}: 1662 (s, $\nu_{C=O}$), 1568 (s, ν_{NO2}), 1342 (s, ν_{NO2}). ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 9.01 (s, 1H, **H_2**); 8.61 (d, 1H, **H_5**, $J_{5\text{-}6}$ = 7.8 Hz); 8.09 (d, 1H, **H_8**, $J_{8\text{-}7}$ = 7.8 Hz); 7.85 (s, 1H, **$H_{2'}$**); 7.49 (dtd, 1H, **H_6 + H_7**, $J_{6\text{-}5} = J_{7\text{-}8}$ = 15.2, Hz $J_{6\text{-}7} = J_{7\text{-}6}$ = 7.1 Hz, $J_{6\text{-}2} = J_{7\text{-}2}$ = 5.8 Hz); 4.42 (t, 2H, **CH_2-N**, $J_{CH2\text{-}CH2}$ = 6.9 Hz); 3.67 (t, 2H, **CH_2-CO**, $J_{CH2\text{-}CH2}$ = 6.9 Hz); 2.65 (s, 3H, **CH_3-Amine**). ^{13}C NMR (DMSO-d_{6j}, 100 MHz) δ ppm: 192.68; 143.81; 140.43; 139.33; 136.03; 135.95; 133.61; 131.87; 125.89; 125.45; 124.56; 122.97; 40.35; 40.19; 10.18. Anal. Calc. for $C_{15}H_{13}N_3O_3S$: C 57.13%, H 4.16%, N 13.33%. Found: C 57.53%, H 3.74%, N 13.12%.

4.4 Compound Handling

Stocks of the synthesised compounds and the reference drug BZ (Sigma-Aldrich) were prepared in 100% DMSO at 50 mM in eppendorf tubes, and stored at 4ºC. Working stocks were prepared in culture medium on the same day as the assay. At final concentration, all the sample wells for the assay contained <0.5% of DMSO. All plates were inspected microscopically to detect contamination or precipitation of the compounds.

4.5 Parasite and Mammalian Cell Cultures

T. cruzi CL-Luc:Neon clone parasites (a bioluminescent:fluorescent derivative of the CL-Brener clone – DTU-VI) were cultured in supplemented RPMI-1640 medium, as described previously [27]. BSR cells (BHK-21 subclone) were cultured in Dulbecco's Modified Eagle's Medium (DMEM, Sigma) supplemented with 5% (v/v) Foetal Bovine Serum (FBS), 100 U/ml of penicillin, and 100 μg/ml streptomycin at 37°C and 5% CO_2. For maintenance, BSR cells were sub-cultured every 3 days at a ratio of 1:5. For the infection of cell monolayers, tissue culture

trypomastigotes (TCTs) were derived from previously infected BSR cells. Cell cultures were exposed to TCTs for 18 h (overnight). Extracellular parasites were then removed by washing with PBS, and the flasks incubated with fresh medium for a further 5–7 days. New extracellular TCTs were isolated by collection and centrifugation of the culture medium at 1600 *g*. Pellets were re-suspended in DMEM with 10% of FBS and kept at 37ºC until use. Motile trypomastigotes were counted using a haemocytometer.

4.6 Biological Assays

4.6.1 Data analysis and definitions

Fluorescence intensities were determined using a BMG FLUOstar Omega (with excitation 488 nm, emission 525 nm for the fluorescent parasites and excitation 530 nm, emission 595 nm for the Alamar blue® assays). Dose-response curves were fitted and 95% confidence intervals were calculated using the sigmoidal dose-response variable slope function from the Graph Pad Prism 8 software (La Jolla California USA, www.graphpad.com). In this study: i) % inhibition of growth is the reduction in the replication rate in the presence of the drug with respect to the untreated controls; ii) IC_{50} is defined as the compound concentration capable of reducing the replication and/or infection by 50% as compared to non-treated controls and values were determined by interpolation from the fitted dose-response curve. Values are expressed as $IC_{50} \pm$ SD; iii) selectivity index (SI) is an indicator of the specificity of growth inhibition of the parasite by the drug, in relation to its inhibition of the host cell; it was calculated as the ratio of host cell:parasite IC_{50} values. For the comet assay, the mean DNA in the tail for each condition was compared with the vehicle control value using the Kruskal-Wallis test followed, if needed, by the post-hoc Bonferroni test. Statistical significance was set at $p<0.05$ in both tests. The Statistics and Data Analysis (STATA) software v12.1 (TX, USA) was used. All determinations were performed in 3 independent experiments with 3 technical replicates per concentration, unless stated otherwise.

4.6.2 In vitro pre-screening assays

Single-point potency assays of 10 μM and 40 μM of drug for epimastigotes and BSR cells, respectively, were set for 72 h exposure. The activity of the drugs was measured by adding 0.125 μg/ml of Alamar Blue® (AB, Laboserv, Giessen,Germany) [38]. AB is reduced by the organisms in a time-dependent process, and plates were incubated for 24 h in the case of the epimastigotes and 6 h in the case of the BSR cells. These incubation times were standardised in our lab, as they depend on the initial plating concentration of the untreated controls. After

incubation, the plates were read at 540 nm. A linear relationship between cellular density and absorbance can be used to determine the growth.

Epimastigotes of *T. cruzi* CL-Luc:Neon clone were seeded at 2.5 x 10^5 parasites per well in 96 well plates in 100 μL of culture medium. To these was added another 100 μL of medium containing 20 μM of drug, to reach a final concentration of 10 μM in the assay. Plates were then incubated at 27ºC for 72 h before addition of AB. BSR cells were seeded at 5 x 10^4 cells per well in 96 well plates in 100 μL of culture medium and allowed to adhere for 6 h at 37˚C and 5% CO_2. Then, another 100 μL medium containing 80 μM drug was added for a final concentration of 40 μM in the assay. The plates were then incubated for an additional 72 h before addition of AB.

4.6.3 In vitro screening and selectivity index

8-point potency curves were generated by serial dilution (2:1) of the drugs in the corresponding culture medium. For epimastigote and BSR cell screening, the seeding and incubation was performed as above for the pre-screenings. For amastigote assays, BSR cells in 100 μL growth medium were added to a black, clear-bottomed, 96-well, lidded, polystyrene microplate at 5 × 10^4 cells/well. After 6 h incubation to allow attachment, cells were infected overnight with 5 × 10^5 TCT/well, a multiplicity of infection (MOI) of 10. The trypomastigote to mammalian cell ratios used were determined empirically, as the minimum ratio necessary to achieve optimal infection levels is statistically distinguishable from background. Next day, wells were washed 3 times with PBS to remove non-internalised trypomastigotes, before adding 200 μL DMEM supplemented with 1% FBS and containing the drugs at the different concentrations. For assessment of activity against amastigote replication, 72 h post-incubation, the plates were washed twice with PBS and fixed with 4% parafolmaldehyde for 30 min. Then, paraformaldehyde was removed, and wells washed with PBS, before taking a fluorescence readout in the BMG FLUOstar Omega plate reader. For trypomastigote screening assays, infective TCTs were isolated from a previously infected culture flask and incubated in eppendorf tubes with the different drug concentrations for 6 h in high-glucose DMEM, supplemented with 10% FBS, at 37ºC. Then, trypomastigotes were washed 3 times with PBS to remove the drug from the medium, and used to infect a plate seeded with BSR cells as above. Non-internalised parasites were removed from the medium on the following day by washing the plates 3 times with PBS, and 200 μL fresh growth medium supplemented with 1% FBS was added. Infection was allowed to progress for an additional 72 h. For assessment of activity against trypomastigotes, we measured the reduction of cell-invasion by quantifying fluorescence

generated by amastigote replication upon successful infection. IC_{50} values were calculated using the Graph Pad Prism 8 software as explained above

4.6.4 Kinetics of killing

Changes in the fluorescence intensity were assessed by daily readouts using the plate reader. For this assay, epimastigotes were seeded as above in 96-well microplates. Growth curves were monitored during the 5 days of exponential growth in the presence of the compounds, until the parasites reached stationary phase (around day 5 after plating). BZ was included as a 'fast-killing' drug control.

4.6.5 Wash-out assays

In vitro infections were carried out as above. However, BSR cells were seeded in 8-well, Ibidi μ-slides with a polymer coverslip, (Cat. No: 80826) or in black, clear-bottomed, 24-well, lidded polystyrene microplates. The concentrations used in these assays were 10x and 20x the IC_{50} value obtained previously for the amastigote form. Infections were divided into two groups for each concentration under study. One group was exposed to the drug for 10 days, while the other group was exposure to the drug for 20 days. Compounds were replaced every 4 days. Relapse day was defined as the first day trypomastigotes could be observed by light microscopy in culture after wash-out of the drug, or replication of amastigotes was observed by fluorescence microscopy. Three wells were prepared per treatment and each individual well was inspected by taking 30 captures per timepoint. These assays allow drugs to be assessed as trypanocidal or trypanostatic.

Images were acquired using an inverted Nikon Eclipse microscope. The chamber/plate containing the infected cells was moved along the x-y plane through a 580 nm LED illumination. Images were collected using a 16-bit, 1-megapixel Pike AVT (F-100B) CCD camera set in the detector plane. An Olympus LMPlanFLN 40x/1.20 objective was used to collect the exit wave leaving the specimen. Imaging was performed by placing the chamber slide/plate on a microscope surrounded by an environmental chamber (OKOLab cage incubator, USA) maintaining the cells and the microscope at 37ºC and 5% CO_2. Sequences were created using the deconvolution app in Nikon imaging software.

4.6.6 Infectivity assays

This assay is a variation of the trypomastigote screening procedure used to determine the efficacy of drugs in preventing infection, either by killing the parasite directly, or by affecting the fitness of the parasite, and blocking infection. Briefly, trypomastigotes are incubated for 6 h in serial drug concentrations, then parasites were washed 3 times with PBS and used to infect the BSR mammalian cells at a MOI of 10:1 (trypomastigote:cell) for 18 h. This allows the concentration that prevents establishment of a productive infection to be determined. Infected BSR cells were readout 120 h post-infection, and chambers were inspected for amastigote replication using an inverted Nikon Eclipse microscope, as explained above.

4.6.7 Drug combination assays

To test drug combinations, the Alamar Blue and fluorescence methods were used to determine the IC_{50} values. Parasites/cells were seeded in the previously described conditions, but the BZ IC_{50} values were re-evaluated in the presence of the IC_{50} of the drug under study. Drug combinations were assessed in triplicate in each plate and repeated at least twice. The combination index (CI) isobologram method was used to analyse the nature of the interaction [39]. A Ci value less than, equal to, or greater than 1 indicates synergism, additivity, and antagonism, respectively.

4.7 Comet Assay

4.7.1 Cell culture

TK-6 cells (human lymphoblastoid cell line) were obtained from the American Type Culture Collection (ATCC). They were grown in RPMI 1640 medium (ATCC modification, ref. A1049101) supplemented with 10% FBS, 100 U/mL penicillin and 0.1 mg/mL streptomycin (all from Gibco). Cells were maintained as a suspension culture in continuous agitation at 37 °C in a humidified atmosphere with 5% CO_2 for no longer than 60 days.

4.7.2 Cell treatment

1 mL containing 6 x 10^5 TK-6 cell suspension was treated with compound **3c** in a 12-well plate, for 3 h. The treatment was performed in the cell culture medium. After that, cells were washed three times in, and then suspended in 1.5 mL of fresh cell culture medium. 0.5 mL of cell suspension was used for analysis and 1 mL for the proliferation assay (**below**). Cells treated with 20 μM MMS were used as a positive control for the Fpg-modified comet assay. Three independent experiments were performed.

4.7.3 Proliferation assay

After cell treatment and wash, cells were resuspended in fresh culture medium and incubated for 48 h, with continuous agitation at 37°C in a humidified atmosphere with 5% CO_2. Cells were counted after 24 h, to adjust the cell concentration, and again at 48 h. The total suspension growth (TSG) was calculated by dividing the number of cells after 48 h by the number of cells just before treatment. Relative suspension growth (RSG) is the relation between the TSG of each treated cell suspension and the TSG of the control cells, expressed as a percentage.

4.7.4 FPG-modified comet assay

The comet assay was carried out using the 12 minigels/slide format and the 12-Gel Comet Assay Units (Norgenotech, Norway) [40,41]. Treated cells were embedded in agarose by mixing 30 μL of cell suspension with 140 μL of 1% low-melting-point agarose in PBS at 37°C. Six 5 μL aliquots, 2 per condition tested, were placed on agarose-pre-coated microscope slides. Slides were immersed in lysis solution (2.5 M NaCl, 0.1 M Na_2EDTA, 0.1 M Tris, pH 10, 1% Triton X-100) for 1 h at 4°C, and then three times, 5 min each, in Fpg reaction buffer (40 mM HEPES, 0.1 M KCl, 0.5 mM EDTA, 0.2 mg/mL BSA, pH 8.0). Each condition (two gels) involved incubation at 37°C for 1 hour with 30 μL of either lysis buffer (without Triton X-100), enzyme reaction buffer, or Fpg. Slides were then immersed in the electrophoresis solution (0.3 M NaOH, 1 mM Na_2EDTA, pH >13) for 40 min at 4°C and electrophoresis was carried out at 1.2 V/cm for an additional 20 min. Slides were then immersed sequentially in DPBS and distilled water for 10 min each, and in 70% and 100% ethanol, 15 min each, before drying overnight.

Comets were stained by adding a drop of 1 μg/mL 4,6-diamidino-2-phenylindole (DAPI) to each mini-gel. The semi-automated image analysis system Comet Assay IV (Perceptive Instruments) was used to measure the percentage of tail DNA of 50 comets per gel (100 comets per condition). The median percentage of DNA in the tail for 100 comets was the descriptor of each condition; gels incubated with the lysis solution (without Triton X-100) represents SBs and alkali labile sites (ALS), and net Fpg-sensitive sites were calculated by subtracting the values in the enzyme reaction buffer from those obtained after the Fpg incubation.

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