

Pyrrolo[1,2-*a*]pyrazine-4,7-dicarboxylates: Synthesis, structural modification, bioactivity prediction, antimicrobial properties, and docking studies

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ABSTRACT

A three-step method for obtaining pyrrolo[1,2-*a*]pyrazine-4,7-dicarboxylates was presented. The method involves the N-alkylation of 5-formylpyrrole-3-carboxylates with bromoacetate, followed by the aminoalkenylation of the N-alkoxycarbonylmethyl group using dimethylformamide di-*tert*-butyl acetal, and further annulation of the pyrazine ring in the presence of ammonium acetate. Procedures for selective hydrolysis, halogenation, arylation, and alkynylation of the synthesized dicarboxylates were described. The *in silico* evaluation of the potential bioactivity of the synthesized dicarboxylates **4a–f**, dicarboxylic acids **7a–c,e**, halogenated dicarboxylates **8f–j**, and dicarboxylic acids **10a–e** was carried out. As seen from the screening of antimicrobial activity, the synthesized compounds **7a–e**, **8c,f–j**, **10a–e** exhibit inhibitory and bactericidal activity against several bacteria and fungi. The highest activity against *Klebsiella pneumonia*, *Staphylococcus aureus*, and *Bacillus subtilis* has been established for the compound **8f** with a MIC of 15.625 µg/mL, and the highest antifungal activity against *Candida albicans* was found for the compounds **8f**, **8g**, and **8i** (MIC=15.625 µg/mL). The molecular docking data show that the compound **8i** has the highest affinity to the ThiM *Klebsiella pneumoniae* kinase, and compounds **8i**, **8j** are noted for their highest affinity to the DNA gyrase from *Staphylococcus aureus*.

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1. Introduction

For a long period, heterocyclic structures have held key positions in the chemical space of organic molecules, as they are crucial for the development of the pharmaceutical industry, agrochemistry, and organic materials science. An important role among them belongs to nitrogen-containing heterocycles, which are essential structural motifs of biologically active substances and pharmaceutical drugs.^{1–5} The widespread use of azoles and other nitrogen heterocycles in drug development is due to their commercial availability, chemical diversity, synthetic tunability, and pronounced tendency toward functionalization.⁶

Over the past decade, condensed azoloazine systems have attracted significant attention in synthetic and medicinal chemistry as promising scaffolds for the development of potential bioactive compounds. Among these, various pyrrolo[1,2-*a*]pyrazine derivatives hold a prominent position.⁷ Reported examples include vasopressin 1b receptor antagonists (**I**),⁸ modulators of the metabotropic receptor mGluR5 (**II**),⁹ a marker for the detection of circulating human cytotoxic T cells, CRTH2 (**III**),¹⁰ inhibitors of proinflammatory secretory phospholipase sPLA-2 (**IV**),¹¹ phosphoinositide 3-kinase PI3K inhibitors (**V**),¹² and cytotoxic agents targeting human lymphoma U937 cells (**VI**) (Fig. 1).¹³

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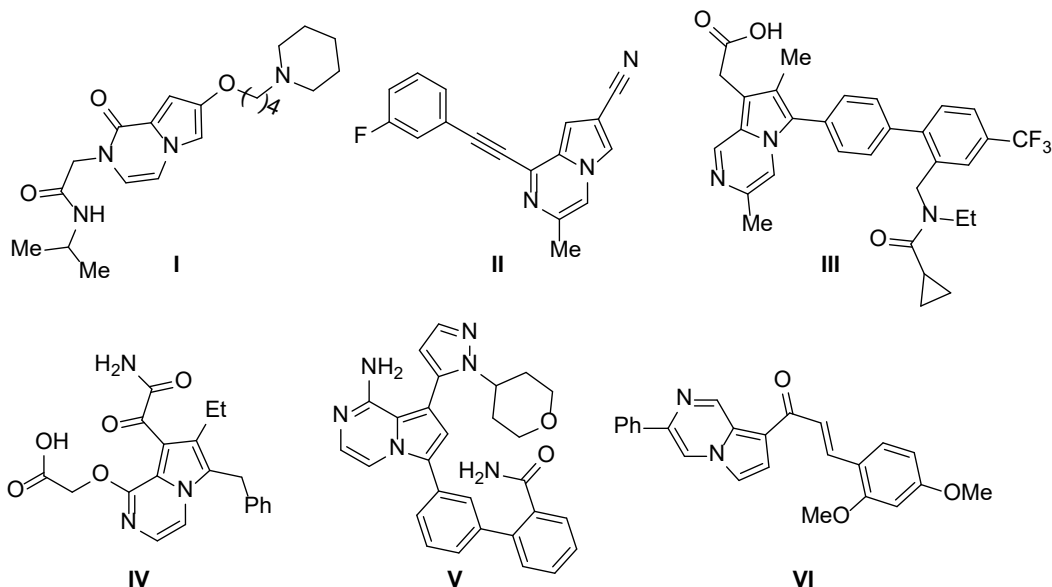


Fig. 1. Selected biologically active pyrrolo[1,2-*a*]pyrazine derivatives

As evidenced by the compounds described above, their pharmacological profiles are largely attributed to structural modifications of the biophoric pyrrolopyrazine bicyclic system. It is reasonable to hypothesize that this scaffold could be further expanded by introducing synthetically versatile groups, such as carboxylates or carboxylic ones, into the pyrrolo[1,2-*a*]pyrazine framework. These functional groups provide valuable handles for subsequent targeted transformations.

Literature reports indicate that pyrrolo[1,2-*a*]pyrazines bearing ester substituents on the pyrrole ring^{9,14-18} exhibit antitumor activity¹⁸ and serve as effective synthetic building blocks for generating mGluR5 antagonists.⁹ Furthermore, their analogues with ester functionalities in the pyrazine ring¹⁹⁻²³ have demonstrated anxiolytic²⁰ and antifungal²³ activity, and have been identified as positive allosteric modulators of metabotropic glutamate receptor 4 (mGluR4).²¹

In light of these findings, the development of a preparatively convenient method for the synthesis of previously unknown pyrrolo[1,2-*a*]pyrazine derivatives bearing carboxylate groups at positions 4 and 7 was deemed justified. This study also explores selected synthetic transformations, bioactivity prediction, antimicrobial screening, and docking studies of the most active compounds.

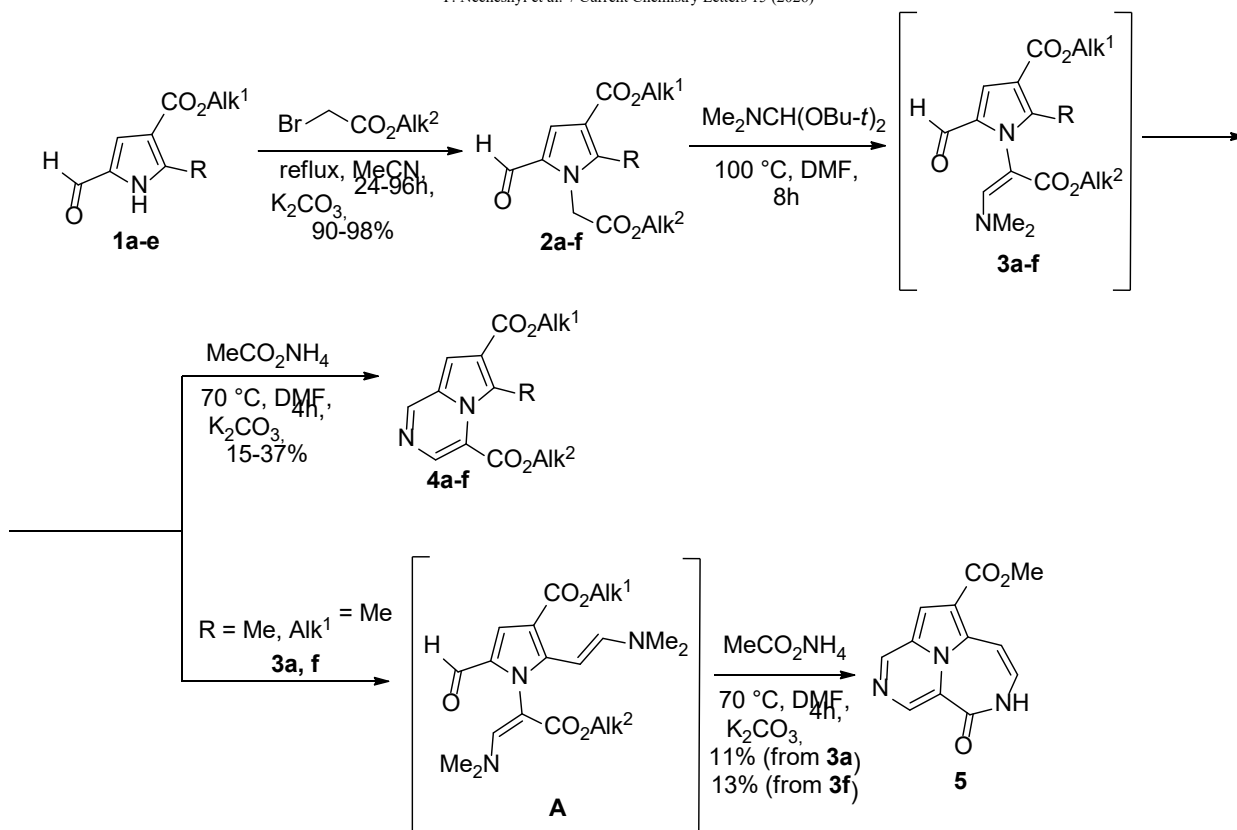
2. Results and Discussion

2.1. Chemistry

Available 5-formyl-1*H*-pyrrole-3-carboxylates **1a–e**²⁴⁻²⁶ were selected as the starting substrates for solving the outlined task. Their reaction with bromoacetates under prolonged reflux in acetonitrile, using K₂CO₃ as a base, afforded the corresponding *N*-alkoxycarbonylmethyl-substituted pyrroles **2a–f** in high yields.

A recent study²⁰ described annulation of a pyrazine ring onto an unsubstituted 3,4,5-pyrrole scaffold *via* sequential treatment of *N*-alkoxycarbonylmethyl-2-formylpyrroles with dimethylformamide dimethyl acetal (DMFDMA) followed by ammonium acetate. In our case, however, DMFDMA proved ineffective as an aminoalkenylation reagent. As an alternative, we employed the di-*tert*-butyl acetal of dimethylformamide (DMFDtBA), which successfully furnished the desired enamino esters **3a–f**.

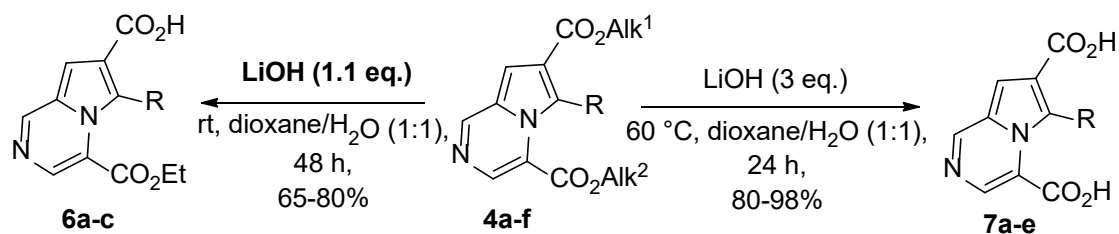
Subsequent reaction of the crude intermediates **3a–f** with MeCO₂NH₄ in DMF at 70 °C in the presence of K₂CO₃ led to the formation of the target pyrrolo[1,2-*a*]pyrazine-4,7-dicarboxylates **4a–f** in moderate overall yields across the two steps. Notably, the cyclization of compounds **2a** and **2f**, bearing a methyl group at the 2-position of the pyrrole ring, displayed a tendency toward a competing side reaction involving this methyl group, which yielded intermediate **A**. Upon treatment with ammonium acetate, the enamino ester moiety of intermediate **A** underwent cyclocondensation involving both the aldehyde and dimethylaminoethenyl groups, affording, in 11–13% yield, the first representative of a previously unknown heterocyclic system: triazabenzoc[*c,d*]azulene **5** (Scheme 1). An experiment in which reaction mixtures of **3a** and **5** were treated with additional portions of DMFDtBA and MeCO₂NH₄ showed no increase in the formation of compound **5**, providing strong evidence in support of the proposed cyclization mechanism.



Compound	R	Alk ¹	Alk ²	Yield by 2, %	Yield by 4, %
1,2a; 3,4a	Me	Me	Et	92	22
1,2b; 3,4b	<i>i</i> -Pr	Me	Et	98	35
1,2c; 3,4c	Ph	Et	Et	90	37
1,2d; 3,4d	4-(OMe)C ₆ H ₄	Me	Et	98	27
1,2e; 3,4e	4-FC ₆ H ₄	Me	Et	95	28
2f; 3,4f	Me	Me	Me	91	15

Scheme 1. Synthesis of pyrrolo[1,2-*a*]pyrazine-4,7-dicarboxylates **4a–f** and 4,7,9b-triazabenzoc[*d*]azulene-1-carboxylate **5**

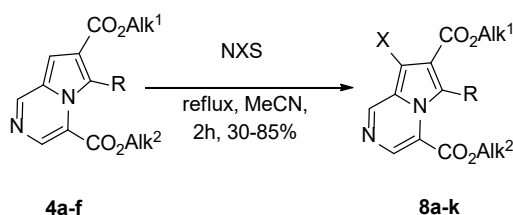
The structures of dicarboxylates **4a–f** were confirmed by IR spectroscopy, ¹H and ¹³C NMR spectroscopy, and chromatography-mass spectrometry. Their IR spectra exhibit strong absorption bands characteristic of carboxyl groups in the range of 1723–1729 cm⁻¹. In the ¹H NMR spectra, in addition to the singlet corresponding to the pyrrole proton at 7.41–7.44 ppm, singlets attributable to pyrazine ring protons 3-H and 1-H appear in the range of 7.88–8.03 ppm and 8.77–8.92 ppm, respectively. The structure of the tricyclic compound **5** was conclusively established by 2D-NMR experiments (see supplementary information). Our investigations into the structural modification of the synthesized pyrrolo[1,2-*a*]pyrazines **4a–f** focused on both ester group transformations and halogenation of the pyrrole ring, followed by functionalization with aryl and alkynyl substituents. Specifically, for carboxylates **4c–e**, treatment with 1.1 eq of LiOH under mild conditions (dioxane/H₂O, 1:1, r.t.) resulted in the selective hydrolysis of the pyrrole ring ester, affording monoacids **6a–c**. Conversely, employing a threefold excess of LiOH and heating the reaction mixture in the same solvent system at 60 °C enabled hydrolysis of both ester groups, producing dicarboxylic acids **7a–e** in nearly quantitative yields (**Scheme 2**).



Compound	R	Yield by 6, %	Yield by 7, %
7a	Me	–	95
7b	<i>i</i> -Pr	–	80
6a, 7c	Ph	76	98
6b, 7d	4-(OMe)C ₆ H ₄	65	90
6c, 7e	4-FC ₆ H ₄	80	95

Scheme 2. Synthesis of 4-(ethoxycarbonyl)pyrrolo[1,2-*a*]pyrazine-7-carboxylic acids **6a–c** and pyrrolo[1,2-*a*]pyrazine-4,7-dicarboxylic acids **7a–e**

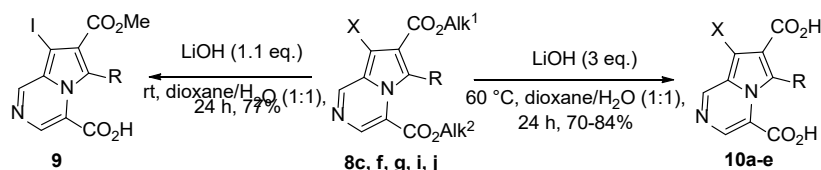
Halogenation of dicarboxylates **4a–f** using N-halosuccinimides (NHS) in refluxing acetonitrile proceeds selectively at the most nucleophilic position 8 of the bicyclic system. Depending on the halogenating agent employed, this reaction affords derivatives **8a–k** in yields ranging from 30% to 85% (Scheme 3). To confirm the position of the halogen atom in **8a–k**, the structure of the compound **8b** was conclusively established by 2D-NMR experiments (see supplementary information).



Compound	R	Alk ¹	Alk ²	X	Yield, %
8a	Me	Me	Et	Cl	31
8b	Me	Me	Et	I	45
8c	Me	Me	Me	Br	85
8d	<i>i</i> -Pr	Me	Et	Cl	30
8e	<i>i</i> -Pr	Me	Et	Br	34
8f	<i>i</i> -Pr	Me	Et	I	52
8g	Ph	Et	Et	Br	57
8h	4-(OMe)C ₆ H ₄	Me	Et	Br	55
8i	4-FC ₆ H ₄	Me	Et	Cl	52
8j	4-FC ₆ H ₄	Me	Et	Br	73
8k	4-FC ₆ H ₄	Me	Et	I	53

Scheme 3. Synthesis of 8-halogenopyrrolo[1,2-*a*]pyrazine-4,7-dicarboxylates **8a–k**

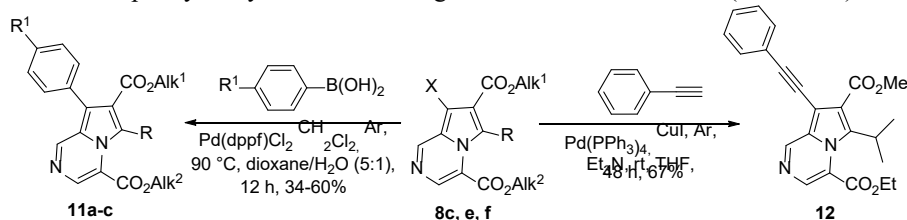
The presence of a halogen atom in the pyrrole ring of compounds **8** markedly influences the mono-hydrolysis reaction. In contrast to the non-halogenated analogs **4**, treatment with 1.1 eq of LiOH under mild conditions yields a mixture of mono- and dicarboxylic acids. Isolation of the mono-hydrolysis product at position 4 – acid **9** – was successful only for carboxylate **8f**. On the other hand, dicarboxylic acids **10a–e** were obtained in high yields through hydrolysis of diesters **8c, f, g, i, j** using an excess of LiOH in a dioxane-water mixture at 60 °C (Scheme 4).



Compound	R	X	Yield, %
10a	Me	Br	80
10b	<i>i</i> -Pr	I	70
10c	Ph	Br	84
10d	4-FC ₆ H ₄	Cl	82
10e	4-FC ₆ H ₄	Br	81

Scheme 4. Synthesis of 8-iodo-7-(methoxycarbonyl)pyrrolo[1,2-*a*]pyrazine-4-carboxylic acid **9** and 8-halogenopyrrolo[1,2-*a*]pyrazine-4,7-dicarboxylic acids **7a–e**

Halogen-substituted pyrrolo[1,2-*a*]pyrazine dicarboxylates **8** can be used as convenient substrates for introducing lipophilic aryl and alkynyl substituents important in medicinal chemistry into the pyrrole ring. On the example of 8-bromo dicarboxylates **8c** and **8e**, it was demonstrated that under Suzuki–Miyaura reaction conditions^{27,28} they undergo cross-coupling with arylboronic acids to form 8-aryl derivatives **11a–c**. Their 8-iodo analogue **8f** was converted into alkynyl derivative **12** by reaction with phenylacetylene under Sonogashira reaction conditions (Scheme 5).²⁹



Compound	R	R ¹	Alk ¹	Alk ²	Yield, %
11a	Me	H	Me	Me	35
11b	<i>i</i> -Pr	NO ₂	Me	Et	34
11c	<i>i</i> -Pr	CF ₃	Me	Et	60

Scheme 5. Synthesis of 8-arylprrrolo[1,2-*a*]pyrazine-4,7-dicarboxylates **11a–c** and 8-alkynylpyrrolo[1,2-*a*]pyrazine-4,7-dicarboxylate **12**.

The structures of the carboxylic acids **6a–c** and **7a–e** derived from dicarboxylates **4a–f**, halogenated dicarboxylates **8a–k**, acids **9** and **10a–e**, as well as 8-aryl(alkynyl) derivatives **11a–c** and **12** were confirmed by IR, ^1H and ^{13}C NMR, and chromatography–mass spectrometry (see Experimental section).

2.2. Bioactivity prediction

The *in silico* evaluation of the potential bioactivity of the synthesized dicarboxylates **4a–f**, dicarboxylic acids **7a–c,e**, halogenated dicarboxylates **8f, g, i, j**, and dicarboxylic acids **10a–e** was carried out using the online platforms SwissADME (<http://www.swissadme.ch>), ProTox 3.0 (<https://tox-new.charite.de>), and MolPredictX (<https://www.molpredictx.ufpb.br>) (see Supplementary Information).

According to the toxicity predictions generated by the ProTox 3.0 platform, all analyzed compounds belong to toxicity class IV (predicted LD_{50} for acute oral toxicity ranges between 1000–2000 mg/kg). Additionally, these compounds satisfy the drug-likeness criteria proposed by Lipinski, Muegge, Ghose, Veber, and Egan, as well as the PAINS filter. Most of them are expected to exhibit good to moderate water solubility. The calculated physicochemical parameters suggest that the analyzed pyrazolo[1,2-*a*]pyrazine dicarboxylates (**4a–c, e**) and their halogenated derivatives (**8c, f, g, i, j**) are capable of crossing the blood–brain barrier (BBB), whereas none of the corresponding acids show this ability. This disagreement likely arises from the significantly higher polarity of the acids, as evidenced by the higher calculated LogP values for the dicarboxylates compared to the acids. Several compounds meet the lead-likeness criteria (**4a, b, 7c, e, 8c, 10a, d**); however, some of them (notably **4c–f, 8f, g, i, j**) do not, primarily due to their elevated molecular weight (>350 g/mol) and high XLOGP3 values (>3.5). It should be noted that in most cases the hydrolysis of diesters improves the predicted biological profile. For instance, acids **7c, e** have no violations according to Brenk or lead-likeness criteria, while corresponding diesters **4c, e** do not meet these criteria.

The MolPredictX platform predicted that the synthesized compounds are likely (with 80–100% probability) to exhibit biological activity against the following pathogens: *Promastigote L. donovani*, *Alzheimer – NADPH*, *Hepatitis C – RNA dependent*, *Trypomastigote Chagas*, *Candida albicans*, *Leishmania major*, *PTR L. major*, *SARS-CoV*, and *Aphis gossypii*.

2.3. Antimicrobial activity

Antimicrobial activity of the synthesized derivatives of pyrrolo[1,2-*a*]pyrazine **7a–e, 8c,f–j**, and **10a–e** was tested *in vitro* against gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis*, gram-negative *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, and fungi *Candida albicans* and *Aspergillus niger*. As seen from the experimental data shown in Table 1, all mentioned derivatives exhibit a moderate antimicrobial activity against these strains. The minimal inhibiting concentration (MIC) for the bacteria ranges between 15.625 – 125 $\mu\text{g/mL}$, and for the fungi, 15.625 – 62.5 $\mu\text{g/mL}$. The highest activity against *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Bacillus subtilis* was found for the compound **8f** with a MIC of 15.625 $\mu\text{g/mL}$. The antibacterial activity against *Pseudomonas aeruginosa* is non-selective, and the MIC is 31.25 $\mu\text{g/mL}$ for all synthesized compounds. The highest antifungal activity against *Candida albicans* was found for the compounds **8f, 8g**, and **8i** (MIC=15.625 $\mu\text{g/mL}$).

Table 1. Antimicrobial activity of pyrrolo[1,2-*a*]pyrazine **7, 8** and **10**

No.	<i>K. pneumoniae</i>	<i>S. aureus</i>	<i>B. subtilis</i>	<i>P. aeruginosa</i>	<i>C. albicans</i>	<i>A. niger</i>
MIC($\mu\text{g/mL}$)						
7a	31.25	62.5	62.5	31.25	31.25	62.5
7b	31.25	125	62.5	31.25	31.25	62.5
7c	31.25	125	62.5	31.25	31.25	62.5
7e	31.25	62.5	125	31.25	31.25	62.5
8c	31.25	125	62.5	31.25	31.25	62.5
8f	15.625	15.625	15.625	31.25	15.625	31.25
8g	31.25	125	62.5	31.25	15.625	31.25
8i	31.25	125	125	31.25	15.625	31.25
8j	31.25	125	62.5	31.25	31.25	62.5
10a	31.25	62.5	62.5	31.25	31.25	31.25
10b	31.25	125	125	31.25	31.25	62.5
10c	31.25	62.5	125	31.25	31.25	31.25
10d	31.25	125	125	31.25	31.25	62.5
10e	31.25	62.5	125	31.25	31.25	62.5
C*	15.625	0.48	0.97	31.25	0.97	0.48

* Decasan (a solution consisting of 0.2 mg/mL of decamethoxin) made by “Yuria-Pharm” was used as an antibacterial control drug. ** Clotrimazole (a solution consisting of 10 mg/mL of clotrimazole) made by PJSC SIC “Borshchahivskiy CPP” was used as an antifungal control drug

2.4. Molecular docking study

Molecular docking was carried out on the kinase ThiM from *Klebsiella pneumoniae* to study the inhibitory activity of the three most active compounds. Since 5-(hydroxyethyl)-methylthiazole kinase (ThiM) of *Klebsiella pneumoniae* is considered an attractive antibacterial target due to its absence in the human body. Still, it plays a key role in the bacterial

thiamine pathway. It is essential in the pathway forming thiamine pyrophosphate (TPP), which is an essential cofactor in bacterial amino acid and carbohydrate metabolic pathways.³⁰ DNA gyrase is an essential enzyme for bacterial survival as it plays a vital role in DNA replication, transcription, and recombination by facilitating the cleavage and rejoining of DNA strands. Different inhibitors target DNA gyrase in *Staphylococcus aureus*, stabilising the gyrase–DNA cleavage complex and preventing the re-ligation of DNA strands, which leads to double-strand breaks and bacterial cell death. That's why DNA gyrase inhibition still contributes significantly to the bactericidal effect.³¹ According to the molecular docking simulation, nine positions were found with the corresponding ligand-protein affinity for every ligand, and their affinities were determined (Table 2). This means compound **8i** is the most affine to *Klebsiella pneumoniae* ThiM kinase, followed by **8g** and **8f**.

Table 2. Ligand-protein interaction of compounds **8f**, **8g**, and **8i** with Kinase ThiM from *Klebsiella pneumoniae* (PDB ID: 6k28).

Parameter	8f	8g	8i
Best binding energy to protein, kcal/mol	-5.8	-6.7	-7.4
Hydrogen bonds	Met49 (2.23 Å)	Gly197 (2.25 Å)	Asn29 (2.64 Å), Met49 (2.06 Å)
Carbon hydrogen bond	Gly71, Met49	Pro47	Pro47
Hydrophobic interactions	Ala101, Ala48	Val100, Ala101, Val31, Val196,	Val196, Val100, Val31, Ala37, Ala48, Ala101
π -Sulphur interaction	–	Met49	Cys200

The analysis of the studied compounds' binding results showed that they bind to the Kinase ThiM protein by polar hydrogen bonds and hydrophobic interactions (**Fig. 1**). In general, all the studied compounds have a different location in the middle of the binding site due to the presence of various functional groups.

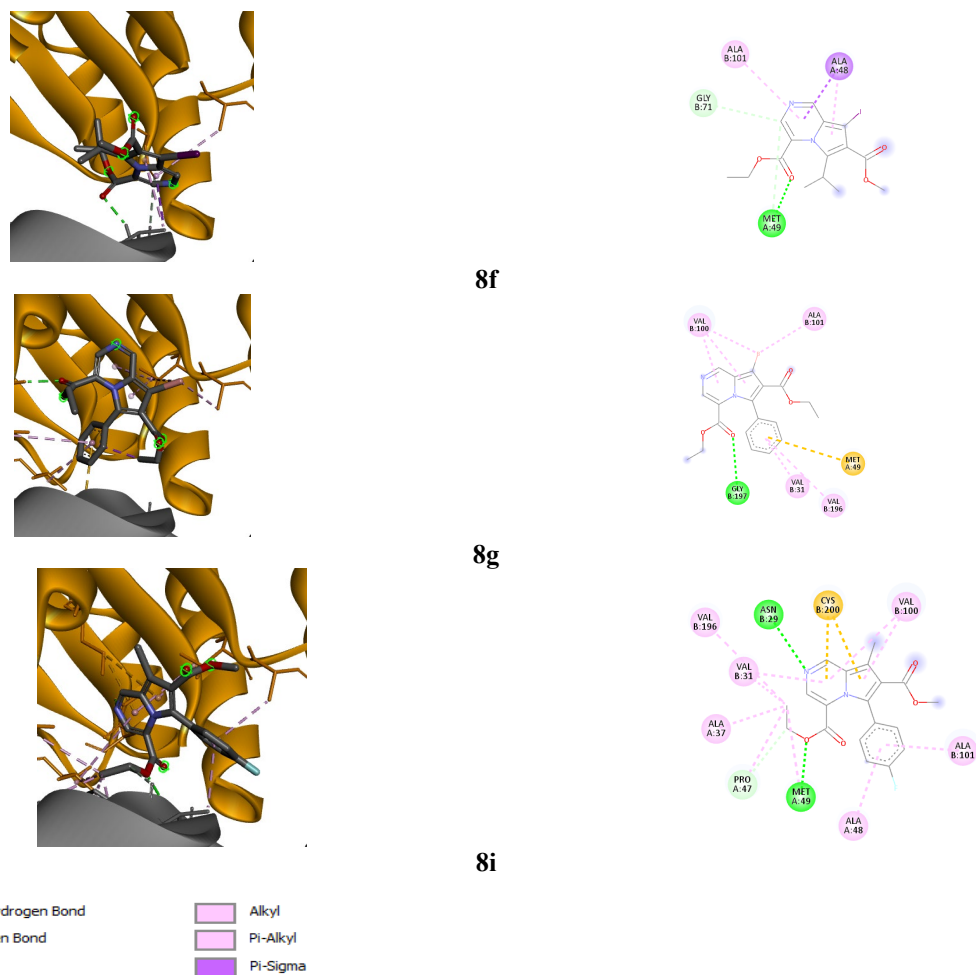


Fig. 1. 3D (left) and 2D (right) schemes of the bonds of **8f**, **8g**, and **8i** inside the active centre of Kinase ThiM from *Klebsiella pneumoniae* (PDB ID: 6k28). Chain A (grey) is shown in the lower part of the figures, and chain B (yellow) is shown in the upper part.

In the molecular docking simulation of DNA gyrase from *Staphylococcus aureus*, nine positions were found with the corresponding ligand-protein affinity for every ligand, and their affinities were determined (Table 3). This means compounds **8i** and **8g** are the most affine, followed by **8f**.

Table 3. Ligand-protein interaction of compounds **8f**, **8g**, and **8i** with DNA gyrase from *Staphylococcus aureus* (PDB ID: 5cdp).

Parameter	8f	8g	8i
Best binding energy to protein, kcal/mol	-7.8	-8.6	-8.6
Hydrogen bonds	–	Ser84 (2.78 Å), Arg122(2.15 Å), DG8(2.95 Å), DG2009(2.80 Å)	Arg122(2.14 Å)
Carbon hydrogen bond	–	–	Arg458
Hydrophobic interactions	DG8, DG2009, DC2013	DC2013, Arg458	DG8, Arg458

The analysis of the interaction of the studied compounds showed that compound **8f** in the active binding site interacts only with the residues of all DNA chains by a non-polar π - π stacked interaction and does not interact with DNA gyrase (**Fig. 2**). Compounds **8g** and **8i** interact with both DNA chains and the protein under study. It should be noted that compound **8g** forms four hydrogen bonds, while compound **8i** forms only one.

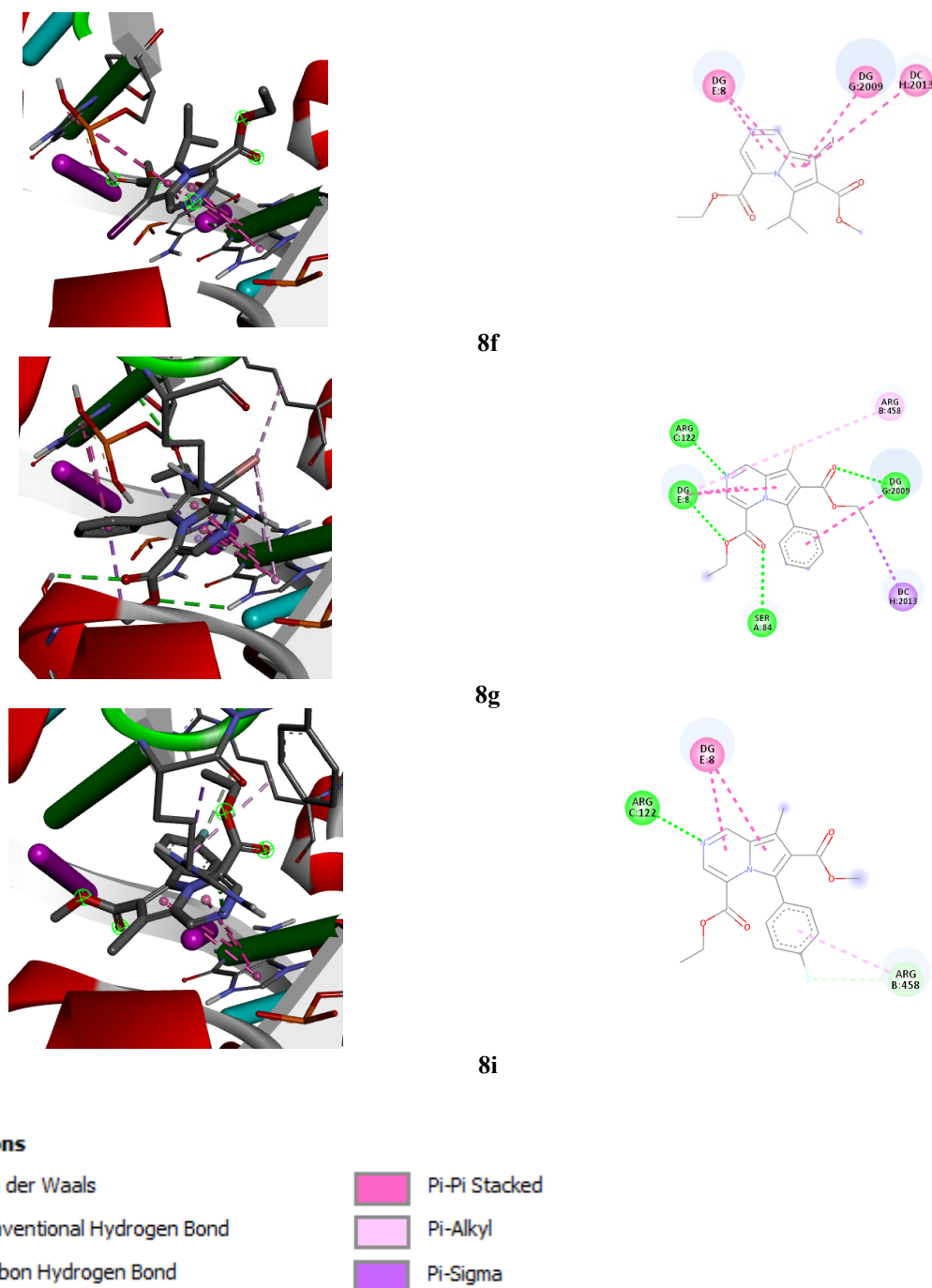


Fig. 2. 3D (left) and 2D (right) schemes of the bonds of **8f**, **8g**, and **8i** inside the active centre of DNA gyrase from *Staphylococcus aureus* (PDB ID: 5cdp).

3. Conclusions

In this work, we have described a method for obtaining new synthetic building blocks of interest in organic and medicinal chemistry – pyrrolo[1,2-*a*]pyrazines functionalized at positions 4 and 7 with carboxylate groups. The approach is based on readily available 5-formylpyrrole-3-carboxylates, which undergo a sequence of straightforward transformations: N-alkylation with bromoacetates, aminoalkenylation of the N-alkoxycarbonylmethyl group using dimethylformamide di-*tert*-butyl acetal, followed by final annulation of the pyrazine ring under the action of ammonium acetate. This sequence provides convenient access to the target pyrrolo[1,2-*a*]pyrazine dicarboxylates. Their synthetic utility was demonstrated through representative transformations, including hydrolysis, halogenation, arylation, and alkynylation. The developed procedures are well suited for generating focused libraries of compounds for subsequent screening studies.

Bioactivity prediction with MolPredictX, carried out against various types of pathogens, indicated a probability of 80–100% for activity against *Promastigote L. donovani*, *Trypomastigote Chagas*, *Candida albicans*, *Leishmania major*, PTR *L. major*, and *Aphis gossypii*. Antimicrobial evaluation of selected compounds confirmed that the highest antibacterial activity against *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Bacillus subtilis* was observed for compound **8f** with a MIC of 15.625 µg/mL. The strongest antifungal activity against *Candida albicans* was found for compounds **8f**, **8g**, and **8i** (MIC = 15.625 µg/mL). In order to study the molecular interactions of the most active compounds **8f**, **8g**, and **8i**, docking studies were performed.

Acknowledgements

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4. Experimental

4.1. Materials and Methods

IR spectra were recorded on a Bruker Vertex 70 spectrometer in KBr pellets. ¹H and ¹³C NMR spectra were recorded on a Varian VXR-400 spectrometer (400, 500, 600 MHz and 100, 125, 150 MHz, respectively) in CDCl₃ (compounds **2a–f**, **4a–f**, **5**, **8a–k**, **11a–c**, **12**) or DMSO-*d*₆ (compounds **6a–c**, **7a–e**, **9**, **10a–e**), with TMS as the internal standard. Mass spectra were recorded on an Agilent LC/MSD SL instrument equipped with a Zorbax SB-C18 column (4.6 × 15 mm, 1.8 µm (PN 82(c)75-932)), solvent DMSO, electrospray ionization. Elemental analysis was performed on a PerkinElmer CHN-analyzer 2400 series instrument in the Analytical Laboratory of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine. Melting points were determined on a Kofler table and were not corrected.

4.2. General procedure

The starting alkyl 2-alkyl(aryl)-1*H*-pyrrole-3-carboxylate for the synthesis of 5-formyl-1*H*-pyrrole-3-carboxylates **1a–e** were provided by Enamine Ltd (Kyiv, Ukraine). The compound **1c**²⁴ was documented earlier, and the compounds **1a**, **b**, **d**, **e**, were synthesized similarly to the method.²⁵

Synthesis of alkyl 1-(2-alkoxy-2-oxoethyl)-5-formyl-2-alkyl(aryl)-1H-pyrrole-3-carboxylates 2a–f To a solution of 5-formylpyrrole-3-carboxylate **1a–e** (30 mmol) in acetonitrile (100 mL), K₂CO₃ (4.98 g, 36 mmol) and the corresponding alkyl bromoacetate (33 mmol) were added sequentially. The reaction mixture was refluxed for 24–96 h, and then concentrated under reduced pressure. The residue was diluted with MTBE (200 mL) and washed with water (200 mL). The aqueous layer was extracted once more with MTBE (100 mL), and the combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The resulting solid was washed with hexane (100 mL).

Synthesis of methyl 1-(1-(dimethylamino)-3-alkoxy-3-oxoprop-1-en-2-yl)-5-formyl-2-alkyl(aryl)-1H-pyrrole-3-carboxylates 3a–f. A mixture of 5-formylpyrrole-3-carboxylate **2a–f** (25 mmol) and N,N-dimethylformamide di-*tert*-butyl acetal (125 mmol, 30.0 mL) in DMF (100 mL) was stirred at 100 °C for 8 h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in MTBE (200 mL) and washed with water (200 mL). The aqueous phase was extracted once more with MTBE (100 mL), and the combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The resulting enaminoesters **3a–f** were used in the next step without further purification.

*Synthesis of 4,7-dialkyl 6-alkyl(aryl)pyrrolo[1,2-*a*]pyrazine-4,7-dicarboxylates 4a–f and methyl 6-oxo-6,7-dihydro-2*a*¹,4,7-triazabenzoc[*c,d*]azulene-1-carboxylate 5.* To a solution of enaminoester **3a–f** in DMF (100 mL), K₂CO₃ (10.37 g, 75 mmol) and NH₄OAc (5.78 g, 75 mmol) were added sequentially. The mixture was stirred at 70 °C for 4 h, cooled to room temperature, and diluted with ethyl acetate (150 mL). The organic phase was washed with water (3 × 150 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel

(hexane/MTBE 7:3). In the case of enaminones **3a** and **3f**, the triazabenzoc[*c,d*]azulene **5** was obtained as a side product and purified by flash chromatography on silica gel (hexane/MTBE 2:8).

Synthesis of 6-arylpyrrolo[1,2-*a*]pyrazine-4,7-dicarboxylic acids 6a–c. To a solution of ester **4c–e** (0.5 mmol) in a 10 mL mixture of dioxane and water (1:1), LiOH (0.013 g, 0.55 mmol) was added, and the mixture was stirred for 48 h. The solvent was removed under reduced pressure, and the residue was dissolved in 1% aqueous LiOH, filtered, and acidified with 10% HCl to pH 4. The resulting precipitate was filtered off, dried, and recrystallized from MeCN/MeOH (1:1).

Synthesis of 6-alkyl(aryl)pyrrolo[1,2-*a*]pyrazine-4,7-dicarboxylic acids 7a–e. To a solution of ester **4a–f** (0.5 mmol) in 10 mL of a dioxane–water mixture (1:1), LiOH (0.036 g, 1.5 mmol) was added, and the mixture was stirred at 60 °C for 24 h. The solvent was removed under reduced pressure, the residue was dissolved in 1% aqueous LiOH, filtered, and acidified with 10% HCl to pH 4. The resulting precipitate was filtered off and dried.

Synthesis of 4,7-dialkyl 8-halogen-6-alkyl(aryl)pyrrolo[1,2-*a*]pyrazine-4,7-dicarboxylates 8a–k. To a solution of ester **4a–f** (3 mmol) in 30 mL of acetonitrile, the corresponding N-halosuccinimide (3.3 mmol) was added, and the mixture was refluxed for 2 h. The solvent was removed under reduced pressure, and the residue was dissolved in MTBE (25 mL) and washed with saturated K₂CO₃ solution (2×25 mL). The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane–MTBE 9:1) for compounds **8d–f**, or by recrystallization from ethanol for compounds **8a–c** and **8g–k**.

Synthesis of 8-iodo-6-isopropyl-7-(methoxycarbonyl)pyrrolo[1,2-*a*]pyrazine-4-carboxylic acid 9. To a solution of ester **8f** (0.208 g, 0.5 mmol) in 10 mL of a dioxane–H₂O mixture (1:1), 0.013 g (0.55 mmol) of LiOH was added, and the mixture was stirred for 24 h. The solvent was removed under reduced pressure, the residue was dissolved in 1% LiOH, filtered, and 10% HCl was added until pH 4 was reached. The resulting precipitate was filtered off and dried.

Synthesis of 8-halogen-6-alkyl(aryl)pyrrolo[1,2-*a*]pyrazine-4,7-dicarboxylic acids 10a–e. To a solution of ester **8c, f, g, i, j** (0.5 mmol) in 10 mL of a dioxane–H₂O mixture (1:1), 0.036 g (1.5 mmol) of LiOH was added. The mixture was stirred at 60 °C for 24 h. The solvent was removed under reduced pressure, the residue was dissolved in 1% LiOH, filtered, and 10% HCl was added until pH 4 was reached. The resulting precipitate was filtered off and dried.

Synthesis of dimethyl 6-alkyl-8-arylpyrrolo[1,2-*a*]pyrazine-4,7-dicarboxylates 11a–c. In an 8 mL vial equipped with a magnetic stir bar, ester **8c, e** (0.5 mmol) was placed, followed by the sequential addition of 4 mL of a dioxane–water mixture (5:1), boronic acid (0.75 mmol), NaHCO₃ (0.168 g, 2 mmol), and Pd(dppf)Cl₂·CH₂Cl₂ (0.041 g, 0.05 mmol). The vial was purged with argon and stirred at 90 °C for 12 h. The solvent was removed under reduced pressure, and the residue was dissolved in 20 mL of ethyl acetate and filtered. The organic layer was washed with water (2×20 mL), and the aqueous phase was extracted once more with ethyl acetate (20 mL). The combined organic layers were dried over Na₂SO₄, concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexane/MTBE 9:1).

Synthesis of 4-ethyl 7-methyl 6-isopropyl-8-(phenylethynyl)pyrrolo[1,2-*a*]pyrazine-4,7-dicarboxylate 12. In an 8 mL vial equipped with a magnetic stir bar, ester **8f** (0.208 g, 0.5 mmol) was added, followed by 4 mL of THF, phenylacetylene (0.066 g, 0.65 mmol), Et₃N (0.1 mL, 0.75 mmol), CuI (0.013 g, 0.07 mmol), and Pd(PPh₃)₄ (0.035 g, 0.03 mmol). The vial was purged with argon and stirred at room temperature for 48 h. The solvent was removed under reduced pressure, and the residue was dissolved in 20 mL of ethyl acetate and filtered. The organic phase was washed with water (2×20 mL), and the aqueous phase was extracted once more with ethyl acetate (20 mL). The combined organic layers were dried over Na₂SO₄, concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexane/MTBE 9:1).

4.3. Physical and Spectral Data

4.3.1. Methyl 1-(2-ethoxy-2-oxoethyl)-5-formyl-2-methyl-1H-pyrrole-3-carboxylate (2a). Yield: 92%, brown solid, mp 83–85 °C. IR spectrum, ν , cm⁻¹: 1672, 1716, 1735 (C=O). ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.26 (3H, t, *J* = 7.2 Hz, OCH₂CH₃), 2.51 (3H, s, CH₃), 3.81 (3H, s, OCH₃), 4.21 (2H, k, *J* = 7.2 Hz, OCH₂CH₃), 5.12 (2H, s, NCH₂), 7.34 (1H, s, H-4), 9.44 (1H, s, CH=O). ¹³C-NMR (100.6 MHz, CDCl₃), δ , ppm: 10.7, 14.1, 46.6, 51.3, 62.0, 114.5, 126.2, 130.6, 145.0, 164.4, 167.6, 179.6. MS, *m/z* (*I*_{rel}, %): 254 [M+H]⁺ (100). Anal. Calcd. for C₁₂H₁₅NO₅ (%): C, 56.91; H, 5.97; N, 5.53. Found: C, 57.06; H, 5.91; N, 5.60.

4.3.2. Methyl 1-(2-ethoxy-2-oxoethyl)-5-formyl-2-isopropyl-1H-pyrrole-3-carboxylate (2b). Yield: 98%, orange oil. ¹H-NMR (400 MHz, CDCl₃), δ , ppm: 1.23 (3H, t, *J* = 7.2 Hz, OCH₂CH₃), 1.33 (6H, d, *J* = 7.2 Hz, CH(CH₃)₂), 3.54–3.65 (1H, m, CH(CH₃)₂), 3.77 (1H, s, OCH₃), 4.18 (2H, k, *J* = 7.2 Hz, OCH₂CH₃), 5.20 (2H, s, NCH₂), 7.34 (1H, s, H-4), 9.40 (1H, s, CH=O). ¹³C-NMR (100.6 MHz, CDCl₃), δ , ppm: 14.1, 19.7 (2C), 25.1, 47.5, 51.3, 61.9, 113.7, 127.7, 130.2, 153.3, 164.1, 167.9, 179.7. MS, *m/z* (*I*_{rel}, %): 282 [M+H]⁺ (100). Anal. Calcd. for C₁₄H₁₉NO₅ (%): C, 59.78; H, 6.81; N, 4.98. Found: C, 59.59; H, 6.83; N, 4.91.

4.3.3. Ethyl 1-(2-ethoxy-2-oxoethyl)-5-formyl-2-phenyl-1H-pyrrole-3-carboxylate (2c). Yield: 90%, yellow oil. ¹H-NMR (500 MHz, CDCl₃), δ , ppm: 1.11 (3H, t, *J* = 7.2 Hz, OCH₂CH₃), 1.23 (3H, t, *J* = 7.2 Hz, OCH₂CH₃), 4.11 (2H, k, *J* = 7.2 Hz, OCH₂CH₃), 4.18 (2H, k, *J* = 7.2 Hz, OCH₂CH₃), 4.81 (2H, s, NCH₂), 7.32 (2H, d, *J* = 7.5 Hz, Ar-H), 7.43–7.47 (3H, m, Ar-H), 7.52 (1H, s, H-4), 9.59 (1H, s, CH=O). ¹³C-NMR (100.6 MHz, CDCl₃), δ , ppm: 14.0, 14.1, 48.0, 60.0, 61.8, 115.8, 125.8, 128.4 (2C), 129.1, 129.7, 130.1 (2C), 131.2, 146.4, 163.2, 168.0, 180.2. MS, *m/z* (*I*_{rel}, %): 330 [M+H]⁺ (100). Anal. Calcd. for C₁₈H₁₉NO₅ (%): C, 65.64; H, 5.81; N, 4.25. Found: C, 65.74; H, 5.75; N, 4.23.

4.3.4. *Methyl 1-(2-ethoxy-2-oxoethyl)-5-formyl-2-(4-methoxyphenyl)-1H-pyrrole-3-carboxylate (2d)*. Yield: 98%, white solid, mp 84–86 °C. IR spectrum, ν , cm^{-1} : 1677, 1713, 1732(C=O). $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ , ppm: 1.23 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 3.68 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.18 (2H, k, $J = 7.2$ Hz, OCH_2CH_3), 4.80 (2H, s, NCH_2), 6.96 (2H, d, $J = 8.8$ Hz, Ar-H), 7.24 (2H, $J = 8.8$ Hz, Ar-H), 7.47 (1H, s, H-4), 9.55 (1H, s, CH=O). $^{13}\text{C-NMR}$ (125.6 MHz, CDCl_3), δ , ppm: 13.6, 47.4, 50.7, 54.8, 61.2, 113.4 (2C), 114.8, 120.3, 125.2, 130.7, 131.0 (2C), 146.1, 160.2, 163.1, 167.5, 179.4. MS, m/z (I_{rel} , %): 346 [$\text{M}+\text{H}$] $^+$ (100). Anal. Calcd. for $\text{C}_{18}\text{H}_{19}\text{NO}_6$ (%): C, 62.60; H, 5.55; N, 4.06. Found: C, 62.61; H, 5.58; N, 4.08.

4.3.5. *Methyl 1-(2-ethoxy-2-oxoethyl)-2-(4-fluorophenyl)-5-formyl-1H-pyrrole-3-carboxylate (2e)*. Yield: 95%, brown oil. $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ , ppm: 1.26 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 3.70 (3H, s, OCH_3), 4.22 (2H, k, $J = 7.2$ Hz, OCH_2CH_3), 4.82 (2H, s, NCH_2), 7.15–7.19 (2H, m, Ar-H), 7.32–7.36 Hz (2H, m, Ar-H), 7.51 (1H, s, H-4), 9.60 (1H, s, CH=O). $^{13}\text{C-NMR}$ (100.6 MHz, CDCl_3), δ , ppm: 14.1, 47.9, 51.3, 61.9, 115.5, 115.7 (2C, d, $^2J_{\text{CF}} = 22.1$ Hz), 124.8 (d, $^4J_{\text{CF}} = 4.0$ Hz), 125.6, 131.3, 132.2 (2C, d, $^3J_{\text{CF}} = 9.1$ Hz), 145.4, 163.5 (CO_2Alk), 163.5 (d, $^1J_{\text{CF}} = 249.5$ Hz), 168.0 (CO_2Alk), 180.2. MS, m/z (I_{rel} , %): 334 [$\text{M}+\text{H}$] $^+$ (100). Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{FNO}_5$ (%): C, 61.26; H, 4.84; N, 4.20. Found: C, 61.05; H, 4.74; N, 4.11.

4.3.6. *Methyl 5-formyl-1-(2-methoxy-2-oxoethyl)-2-methyl-1H-pyrrole-3-carboxylate (2f)*. Yield: 91%, white solid, mp 105–106 °C. IR spectrum, ν , cm^{-1} : 1679, 1715, 1730 (C=O). $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ , ppm: 2.54 (1H, s, CH_3), 3.79 (1H, s, OCH_3), 3.84 (1H, s, OCH_3), 5.18 (2H, s, NCH_2), 7.38 (1H, s, H-4), 9.47 (1H, s, CH=O). $^{13}\text{C-NMR}$ (100.6 MHz, CDCl_3), δ , ppm: 10.7, 46.5, 51.3, 52.8, 114.6, 126.2, 130.6, 145.0, 164.4, 168.1, 179.7. MS, m/z (I_{rel} , %): 240 [$\text{M}+\text{H}$] $^+$ (100). Anal. Calcd. for $\text{C}_{11}\text{H}_{13}\text{NO}_5$ (%): C, 55.23; H, 5.48; N, 5.86. Found: C, 55.29; H, 5.55; N, 5.82.

4.3.7. *4-Ethyl 7-methyl 6-methylpyrrolo[1,2-a]pyrazine-4,7-dicarboxylate (4a)*. Yield: 22%, greenish yellow solid, mp 92–93 °C. IR spectrum, ν , cm^{-1} : 1729 (C=O). $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ , ppm: 1.42 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 2.64 (3H, s, CH_3), 3.89 (3H, s, OCH_3), 4.46 (2H, k, $J = 7.2$ Hz, OCH_2CH_3), 7.41 (1H, s, H-8), 8.02 (1H, s, H-3), 8.82 (1H, s, H-1). $^{13}\text{C-NMR}$ (150.8 MHz, CDCl_3), δ , ppm: 14.0, 14.2, 51.6, 62.3, 109.1, 119.8, 121.2, 128.3, 131.5, 134.1, 149.0, 162.2, 164.9. MS, m/z (I_{rel} , %): 263 [$\text{M}+\text{H}$] $^+$ (100). Anal. Calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_4$ (%): C, 59.54; H, 5.38; N, 10.68. Found: C, 59.65; H, 5.43; N, 10.60.

4.3.8. *4-Ethyl 7-methyl 6-isopropylpyrrolo[1,2-a]pyrazine-4,7-dicarboxylate (4b)*. Yield: 35%, greenish yellow solid, mp 110–112 °C. IR spectrum, ν , cm^{-1} : 1725(C=O). $^1\text{H-NMR}$ (500 MHz, CDCl_3), δ , ppm: 1.43 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 1.47 (6H, d, 7.2 Hz, $\text{CH}(\text{CH}_3)_2$), 3.08–3.17 (1H, m, $\text{CH}(\text{CH}_3)_2$), 3.90 (3H, s, OCH_3), 4.46 (2H, k, $J = 7.2$ Hz, OCH_2CH_3), 7.47 (1H, s, H-8), 7.91 (1H, s, H-3), 8.77 (1H, s, H-1). $^{13}\text{C-NMR}$ (100.6 MHz, CDCl_3), δ , ppm: 14.1, 19.5 (2C), 28.4, 51.8, 62.4, 111.4, 119.6, 121.6, 127.5, 134.3, 140.6, 149.4, 163.6, 164.5. MS, m/z (I_{rel} , %): 291 [$\text{M}+\text{H}$] $^+$ (100). Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_4$ (%): C, 62.06; H, 6.25; N, 9.65. Found: C, 61.90; H, 6.30; N, 9.76.

4.3.9. *Diethyl 6-phenylpyrrolo[1,2-a]pyrazine-4,7-dicarboxylate (4c)*. Yield: 37%, greenish yellow solid, mp 82–83 °C. IR spectrum, ν , cm^{-1} : 1727 (C=O). $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ , ppm: 1.10 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 1.25 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 3.65 (2H, k, $J = 7.2$ Hz, OCH_2CH_3), 4.25 (2H, k, $J = 7.2$ Hz, OCH_2CH_3), 7.42–7.49 (5H, m, Ar-H), 7.56 (1H, s, H-8), 7.88 (1H, s, H-3), 8.92 (1H, s, H-1). $^{13}\text{C-NMR}$ (100.6 MHz, CDCl_3), δ , ppm: 13.8, 14.1, 60.6, 62.0, 109.3, 120.7, 122.1, 128.2 (2C), 128.4, 129.0, 129.2 (2C), 131.2, 131.7, 133.2, 149.2, 161.9, 163.8. MS, m/z (I_{rel} , %): 339 [$\text{M}+\text{H}$] $^+$ (100). Anal. Calcd. for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_4$ (%): C, 67.44; H, 5.36; N, 8.28. Found: C, 67.55; H, 5.39; N, 8.40.

4.3.10. *4-Ethyl 7-methyl 6-(4-methoxyphenyl)pyrrolo[1,2-a]pyrazine-4,7-dicarboxylate (4d)*. Yield: 27%, yellow-orange solid, mp 123–125 °C. IR spectrum, ν , cm^{-1} : 1729 (C=O). $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ , ppm: 1.13 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 3.74 (2H, k, $J = 7.2$ Hz, OCH_2CH_3), 3.80 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 7.00 (2H, d, $J = 8.8$ Hz, Ar-H), 7.36 (2H, d, $J = 8.8$ Hz, Ar-H), 7.54 (1H, s, H-8), 7.86 (1H, s, H-3), 8.90 (1H, s, H-1). $^{13}\text{C-NMR}$ (100.6 MHz, CDCl_3), δ , ppm: 13.9, 51.7, 55.4, 62.2, 109.6, 113.7 (2C), 120.2, 122.2, 123.1, 128.2, 130.5 (2C), 132.3, 132.7, 148.9, 160.1, 161.8, 164.2. MS, m/z (I_{rel} , %): 355 [$\text{M}+\text{H}$] $^+$ (100). Anal. Calcd. for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_5$ (%): C, 64.40; H, 5.12; N, 7.91. Found: C, 64.25; H, 5.19; N, 7.83.

4.3.11. *4-Ethyl 7-methyl 6-(4-fluorophenyl)pyrrolo[1,2-a]pyrazine-4,7-dicarboxylate (4e)*. Yield: 28%, yellow-orange solid, mp 100–101 °C. IR spectrum, ν , cm^{-1} : 1724 (C=O). $^1\text{H-NMR}$ (500 MHz, CDCl_3), δ , ppm: 1.13 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 3.74–3.78 (5H, m, $\text{OCH}_2\text{CH}_3 + \text{OCH}_3$), 7.13–7.17 (2H, m, Ar-H), 7.38–7.40 (2H, m, Ar-H), 7.52 (1H, s, H-8), 7.88 (1H, s, H-3), 8.91 (1H, s, H-1). $^{13}\text{C-NMR}$ (125.6 MHz, CDCl_3), δ , ppm: 13.3, 51.2, 61.6, 108.7, 114.9 (2C, d, $^2J_{\text{CF}} = 22.6$ Hz), 119.9, 121.4, 126.7 (d, $^4J_{\text{CF}} = 3.8$ Hz), 127.9, 130.4, 130.7 (2C, d, $^3J_{\text{CF}} = 7.5$ Hz), 132.9, 148.7, 161.5 (CO_2Alk), 162.3 (d, $^1J_{\text{CF}} = 305.2$ Hz), 163.4 (CO_2Alk). MS, m/z (I_{rel} , %): 343 [$\text{M}+\text{H}$] $^+$ (100). Anal. Calcd. for $\text{C}_{18}\text{H}_{15}\text{FN}_2\text{O}_4$ (%): C, 63.15; H, 4.42; N, 8.18. Found: C, 63.11; H, 4.37; N, 8.12.

4.3.12. *Dimethyl 6-methylpyrrolo[1,2-a]pyrazine-4,7-dicarboxylate (4f)*. Yield: 15%, yellow-orange solid, mp 161–163 °C. IR spectrum, ν , cm^{-1} : 1722 (C=O). $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ , ppm: 2.63 (1H, s, CH_3), 3.89 (1H, s, OCH_3), 3.99 (1H, s, OCH_3), 7.42 (1H, s, H-8), 8.03 (1H, s, H-3), 8.82 (1H, s, H-1). $^{13}\text{C-NMR}$ (125.6 MHz, CDCl_3), δ , ppm: 13.5, 51.2, 52.4,

108.8, 119.4, 120.3, 127.8, 131.1, 133.8, 148.6, 162.1, 164.4. MS, m/z (I_{rel} , %): 249 $[M+H]^+$ (100). Anal. Calcd. for $C_{12}H_{12}N_2O_4$ (%): C, 58.06; H, 4.87; N, 11.29. Found: C, 58.19; H, 4.94; N, 11.37.

4.3.13. Methyl 6-oxo-6,7-dihydro-2a',4,7-triazabenzoc[cd]azulene-1-carboxylate (5). Yield: 11% (from **2a**), 13% (from **2f**), dark brown solid, mp 240-243 °C (decomposition). IR spectrum, ν , cm^{-1} : 1659, 1721 (C=O), 3277 (NH). 1H -NMR (600 MHz, DMSO- d_6), δ , ppm: 3.75 (3H, s, OCH₃), 5.48 (1H, dd, $J_1 = 10.2$ Hz, $J_2 = 6.6$ Hz, H-8), 6.12 (1H, d, $J = 10.2$ Hz, H-9), 7.00 (1H, s, H-2), 7.66 (1H, s, H-5), 8.45 (1H, s, H-3), 9.45 (1H, d, $J = 6.6$ Hz, NH). ^{13}C -NMR (150.8 MHz, DMSO- d_6), δ , ppm: 52.0, 99.3, 108.6, 114.7, 124.6, 125.2, 129.0, 131.1, 135.3, 152.9, 160.3, 164.1. MS, m/z (I_{rel} , %): 244 $[M+H]^+$ (100). Anal. Calcd. for $C_{12}H_9N_3O_3$ (%): C, 59.26; H, 3.73; N, 17.28. Found: C, 59.16; H, 3.77; N, 17.31.

4.3.14. 4-(Ethoxycarbonyl)-6-phenylpyrrolo[1,2-a]pyrazine-7-carboxylic acid (6a). Yield: 76%, green solid, mp 240-242 °C. IR spectrum, ν , cm^{-1} : 1708, 1742 (C=O), 2365-2720 (COOH), 3432 (OH). 1H -NMR (400 MHz, DMSO- d_6), δ , ppm: 1.01 (3H, t, $J = 7.2$ Hz, OCH₂CH₃), 3.56 (2H, k, $J = 7.2$ Hz, OCH₂CH₃), 7.42-7.48 (5H, m, Ar-H), 8.00 (1H, s, H-8), 8.04 (1H, s, H-3), 9.45 (1H, s, H-1). The protons of the COOH group are in exchange with the water molecules of the DMSO- d_6 . ^{13}C -NMR (150.8 MHz, DMSO- d_6), δ , ppm: 13.9, 62.7, 116.2, 123.1, 124.2, 126.9, 127.9, 128.6 (2C), 129.5 (2C), 129.8, 130.4, 134.9, 146.0, 160.4, 164.2. MS, m/z (I_{rel} , %): 311 $[M+H]^+$ (100). Anal. Calcd. for $C_{17}H_{14}N_2O_4$ (%): C, 65.80; H, 4.55; N, 9.03. Found: C, 65.77; H, 4.47; N, 9.07.

4.3.15. 4-(Ethoxycarbonyl)-6-(4-methoxyphenyl)pyrrolo[1,2-a]pyrazine-7-carboxylic acid (6b). Yield: 65, yellow solid, mp 250-252 °C (decomposition). IR spectrum, ν , cm^{-1} : 1710, 1745 (C=O), 2354-2705 (COOH), 3437 (OH). 1H -NMR (400 MHz, DMSO- d_6), δ , ppm: 1.03 (3H, t, $J = 7.2$ Hz, OCH₂CH₃), 3.62 (2H, k, $J = 7.2$ Hz, OCH₂CH₃), 3.80 (3H, s, OCH₃), 7.00 (2H, d, $J = 8.8$ Hz, Ar-H), 7.32 (2H, d, $J = 8.8$ Hz, Ar-H), 7.73 (1H, s, H-8), 7.90 (1H, s, H-3), 9.19 (1H, s, H-1). The protons of the COOH group are in exchange with the water molecules of the DMSO- d_6 . ^{13}C -NMR (150.8 MHz, DMSO- d_6), δ , ppm: 13.9, 55.7, 62.4, 111.6, 114.0 (2C), 119.2, 121.9, 122.4, 123.1, 128.0, 131.1 (2C), 132.4, 148.8, 160.1, 161.4, 164.8. MS, m/z (I_{rel} , %): 341 $[M+H]^+$ (100). Anal. Calcd. for $C_{18}H_{16}N_2O_5$ (%): C, 63.52; H, 4.74; N, 8.23. Found: C, 63.65; H, 4.79; N, 8.14.

4.3.16. 4-(Ethoxycarbonyl)-6-(4-fluorophenyl)pyrrolo[1,2-a]pyrazine-7-carboxylic acid (6c). Yield: 80%, yellow solid, mp >250 °C. IR spectrum, ν , cm^{-1} : 1707, 1741 (C=O), 2377-2732 (COOH), 3441 (OH). 1H -NMR (300 MHz, DMSO- d_6), δ , ppm: 1.05 (3H, t, $J = 7.2$ Hz, OCH₂CH₃), 3.65 (2H, k, $J = 7.2$ Hz, OCH₂CH₃), 7.26-7.32 (2H, m, Ar-H), 7.41-7.47 (2H, m, Ar-H), 7.62 (1H, s, H-8), 7.90 (1H, s, H-3), 9.13 (1H, s, H-1). The protons of the COOH group are in exchange with the water molecules of the DMSO- d_6 . ^{13}C -NMR (125.6 MHz, DMSO- d_6), δ , ppm: 13.5, 61.7, 109.3, 114.9 (2C, d, $^2J_{CF} = 21.4$ Hz), 121.4, 121.5, 127.4 (d, $^4J_{CF} = 2.5$ Hz), 127.9, 129.6, 131.6 (2C, d, $^3J_{CF} = 7.5$ Hz), 132.6, 149.4, 161.1, 162.1 (d, $^1J_{CF} = 236.1$ Hz), 164.5. MS, m/z (I_{rel} , %): 329 $[M+H]^+$ (100). Anal. Calcd. for $C_{17}H_{13}FN_2O_4$ (%): C, 62.19; H, 3.99; N, 8.53. Found: C, 62.28; H, 3.93; N, 8.39.

4.3.17. 6-Methylpyrrolo[1,2-a]pyrazine-4,7-dicarboxylic acid (7a). Yield: 95%, brown solid, mp >250 °C. IR spectrum, ν , cm^{-1} : 1708 (C=O), 2465-2729 (COOH), 3435 (OH). 1H -NMR (400 MHz, DMSO- d_6), δ , ppm: 2.58 (3H, s, CH₃), 7.45 (1H, s, H-8), 7.98 (1H, s, H-3), 8.98 (1H, s, H-1). The protons of the COOH group are in exchange with the water molecules of the DMSO- d_6 . ^{13}C -NMR (125.6 MHz, DMSO- d_6), δ , ppm: 14.0, 110.1, 120.9, 122.5, 128.2, 131.2, 132.2, 148.9, 163.6, 165.9. MS, m/z (I_{rel} , %): 221 $[M+H]^+$ (100). Anal. Calcd. for $C_{10}H_8N_2O_4$ (%): C, 54.55; H, 3.66; N, 12.72. Found: C, 54.67; H, 3.62; N, 12.75.

4.3.18. 6-Isopropylpyrrolo[1,2-a]pyrazine-4,7-dicarboxylic acid (7b). Yield: 80%, white solid, mp 225-227 °C (decomposition). IR spectrum, ν , cm^{-1} : 1706 (C=O), 2465-2729 (COOH), 3435 (OH). 1H -NMR (400 MHz, DMSO- d_6), δ , ppm: 1.41 (6H, d, $J = 7.2$ Hz, CH(CH₃)₂), 3.17-3.27 (1H, m, CH(CH₃)₂), 7.56 (1H, s, H-8), 7.91 (1H, s, H-3), 8.98 (1H, s, H-1). The protons of the COOH group are in exchange with the water molecules of the DMSO- d_6 . ^{13}C -NMR (125.6 MHz, DMSO- d_6), δ , ppm: 19.4 (2C), 27.7, 112.5, 120.9, 122.4, 126.8, 131.1, 139.9, 148.2, 164.2, 165.1. MS, m/z (I_{rel} , %): 249 $[M+H]^+$ (100). Anal. Calcd. for $C_{12}H_{12}N_2O_4$ (%): C, 58.06; H, 4.87; N, 11.29. Found: C, 58.09; H, 4.96; N, 11.40.

4.3.19. 6-Phenylpyrrolo[1,2-a]pyrazine-4,7-dicarboxylic acid (7c). Yield: 98%, pale-green solid, mp 249-251 °C (decomposition). IR spectrum, ν , cm^{-1} : 1710 (C=O), 2417-2708 (COOH), 3435 (OH). 1H -NMR (400 MHz, DMSO- d_6), δ , ppm: 7.30-7.36 (5H, m, Ar-H), 7.53 (1H, s, H-8), 7.83 (1H, s, H-3), 9.03 (1H, s, H-1). The protons of the COOH group are in exchange with the water molecules of the DMSO- d_6 . ^{13}C -NMR (125.6 MHz, DMSO- d_6), δ , ppm: 109.4, 120.8, 122.4, 127.8 (2C), 128.0, 128.4, 129.0 (2C), 131.2, 131.3, 132.3, 149.0, 162.2, 164.6. MS, m/z (I_{rel} , %): 283 $[M+H]^+$ (100). Anal. Calcd. for $C_{15}H_{10}N_2O_4$ (%): C, 63.83; H, 3.57; N, 9.92. Found: C, 63.96; H, 3.61; N, 9.81.

4.3.20. 6-(4-Methoxyphenyl)pyrrolo[1,2-a]pyrazine-4,7-dicarboxylic acid (7d). Yield: 90%, yellow solid, mp 240-243 °C (decomposition). IR spectrum, ν , cm^{-1} : 1710 (C=O), 2417-2708 (COOH), 3435 (OH). 1H -NMR (400 MHz, DMSO- d_6), δ , ppm: 3.76 (3H, s, OCH₃), 6.92 (2H, d, $J = 8.8$ Hz, Ar-H), 7.24 (2H, d, $J = 8.8$ Hz, Ar-H), 7.50 (1H, s, H-8), 7.79 (1H, s, H-3), 8.99 (1H, s, H-1). The protons of the COOH group are in exchange with the water molecules of the DMSO- d_6 . ^{13}C -NMR (125.6 MHz, DMSO- d_6), δ , ppm: 55.6, 109.7, 113.8 (2C), 121.1, 123.1, 124.0, 128.3, 131.0 (2C), 131.8, 132.5, 149.5, 159.8,

162.9, 165.2. MS, m/z (I_{rel} , %): 313 $[M+H]^+$ (100). Anal. Calcd. for $C_{16}H_{12}N_2O_5$ (%): C, 61.54; H, 3.87; N, 8.97. Found: C, 61.44; H, 3.77; N, 9.09.

4.3.21. *6-(4-Fluorophenyl)pyrrolo[1,2-a]pyrazine-4,7-dicarboxylic acid (7e)*. Yield: 95%, yellow solid, mp >250 °C. IR spectrum, ν , cm^{-1} : 1711 (C=O), 2426-2731 (COOH), 3440 (OH). 1H -NMR (400 MHz, DMSO- d_6), δ , ppm: 7.22-7.25 (2H, m, Ar-H), 7.39-7.42 (2H, m, Ar-H), 7.59 (1H, s, H-8), 7.88 (1H, s, H-3), 9.09 (1H, s, H-1). The protons of the COOH group are in exchange with the water molecules of the DMSO- d_6 . ^{13}C -NMR (125.6 MHz, DMSO- d_6), δ , ppm: 110.1, 115.3 (2C, d, $^2J_{CF}$ = 21.4 Hz), 121.6, 122.9, 128.2 (d, $^4J_{CF}$ = 2.5 Hz), 128.5, 130.8, 132.0 (2C, d, $^3J_{CF}$ = 7.5 Hz), 132.4, 149.3, 162.6 (d, $^1J_{CF}$ = 244.9 Hz), 162.7, 165.0. MS, m/z (I_{rel} , %): 301 $[M+H]^+$ (100). Anal. Calcd. for $C_{15}H_9FN_2O_4$ (%): C, 60.01; H, 3.02; N, 9.33. Found: C, 60.09; H, 3.07; N, 9.30.

4.3.22. *4-Ethyl 7-methyl 8-chloro-6-methylpyrrolo[1,2-a]pyrazine-4,7-dicarboxylate (8a)*. Yield: 31%, greenish yellow solid, mp 98-99 °C. IR spectrum, ν , cm^{-1} : 1717 (C=O). 1H -NMR (400 MHz, $CDCl_3$), δ , ppm: 1.46 (3H, t, J = 7.2 Hz, OCH_2CH_3), 2.63 (3H, s, CH_3), 3.98 (3H, s, OCH_3), 4.49 (2H, k, J = 7.2 Hz, OCH_2CH_3), 8.09 (1H, s, H-3), 8.97 (1H, s, H-1). ^{13}C -NMR (150.8 MHz, $CDCl_3$), δ , ppm: 14.1, 14.6, 51.9, 62.5, 111.7, 117.5, 120.7, 125.5, 131.3, 134.7, 147.1, 161.8, 163.7. MS, m/z (I_{rel} , %): 297 $[M+H]^+$ (100). Anal. Calcd. for $C_{13}H_{13}ClN_2O_4$ (%): C, 52.62; H, 4.42; N, 9.44. Found: C, 52.76; H, 4.41; N, 9.31.

4.3.23. *4-Ethyl 7-methyl 8-iodo-6-methylpyrrolo[1,2-a]pyrazine-4,7-dicarboxylate (8b)*. Yield: 45%, orange brown solid, mp 120-121 °C. IR spectrum, ν , cm^{-1} : 1713 (C=O). 1H -NMR (600 MHz, $CDCl_3$), δ , ppm: 1.44 (3H, t, J = 7.2 Hz, OCH_2CH_3), 2.62 (3H, s, CH_3), 3.96 (3H, s, OCH_3), 4.47 (2H, k, J = 7.2 Hz, OCH_2CH_3), 8.09 (1H, s, H-3), 8.89 (1H, s, H-1). ^{13}C -NMR (150.8 MHz, $CDCl_3$) δ (ppm): 14.2, 14.9, 51.7, 62.5, 63.8, 121.3, 122.4, 129.7, 132.7, 135.0, 150.2, 161.6, 163.9. MS, m/z (I_{rel} , %): 389 $[M+H]^+$ (100). Anal. Calcd. for $C_{13}H_{13}IN_2O_4$ (%): C, 40.23; H, 3.38; N, 7.22. Found: C, 40.29; H, 3.39; N, 7.17.

4.3.24. *Dimethyl 8-bromo-6-methylpyrrolo[1,2-a]pyrazine-4,7-dicarboxylate (8c)*. Yield: 85%, brown solid, mp 138-139 °C. IR spectrum, ν , cm^{-1} : 1713 (C=O). 1H -NMR (400 MHz, $CDCl_3$), δ , ppm: 2.58 (1H, s, CH_3), 3.93 (1H, s, OCH_3), 3.98 (1H, s, OCH_3), 8.06 (1H, s, H-3), 8.90 (1H, s, H-1). ^{13}C -NMR (125.6 MHz, $CDCl_3$), δ , ppm: 14.1, 51.3, 52.6, 96.2, 118.8, 120.0, 126.4, 131.3, 134.8, 148.0, 161.7, 163.3. MS, m/z (I_{rel} , %): 327 $[M+H]^+$ (100). Anal. Calcd. for $C_{12}H_{11}BrN_2O_4$ (%): C, 44.06; H, 3.39; N, 8.56. Found: C, 44.19; H, 3.30; N, 8.70.

4.3.25. *4-Ethyl 7-methyl 8-chloro-6-isopropylpyrrolo[1,2-a]pyrazine-4,7-dicarboxylate (8d)*. Yield: 30%, green solid, mp 57-58 °C. IR spectrum, ν , cm^{-1} : 1717 (C=O). 1H -NMR (400 MHz, $CDCl_3$), δ , ppm: 1.37-1.43 (9H, m, OCH_2CH_3 + $CH(CH_3)_2$), 3.07-3.17 (1H, m, $CH(CH_3)_2$), 3.95 (3H, s, OCH_3), 4.44 (2H, k, J = 7.2 Hz, OCH_2CH_3), 7.93 (1H, s, H-3), 8.86 (1H, s, H-1). ^{13}C -NMR (400 MHz, $CDCl_3$), δ , ppm: 14.1, 20.3 (2C), 28.4, 52.3, 62.7, 111.8, 118.8, 121.2, 124.6, 134.5, 138.5, 147.0, 163.0, 164.2. MS, m/z (I_{rel} , %): 325 $[M+H]^+$ (100). Anal. Calcd. for $C_{15}H_{17}ClN_2O_4$ (%): C, 55.48; H, 5.28; N, 8.63. Found: C, 55.39; H, 5.33; N, 8.61.

4.3.26. *4-Ethyl 7-methyl 8-bromo-6-isopropylpyrrolo[1,2-a]pyrazine-4,7-dicarboxylate (8e)*. Yield: 34%, greenish yellow solid, mp 68-70 °C. IR spectrum, ν , cm^{-1} : 1714 (C=O). 1H -NMR (400 MHz, $CDCl_3$), δ , ppm: 1.35-1.42 (9H, m, OCH_2CH_3 + $CH(CH_3)_2$), 3.08-3.18 (1H, m, $CH(CH_3)_2$), 3.94 (3H, s, OCH_3), 4.43 (2H, k, J = 7.2 Hz, OCH_2CH_3), 7.94 (1H, s, H-3), 8.83 (1H, s, H-1). ^{13}C -NMR (100.6 MHz, $CDCl_3$), δ , ppm: 14.1, 20.5 (2C), 28.3, 52.3, 62.7, 96.9, 120.8, 121.4, 126.0, 134.6, 138.7, 148.2, 163.0, 164.6. MS, m/z (I_{rel} , %): 369 $[M+H]^+$ (100). Anal. Calcd. for $C_{15}H_{17}BrN_2O_4$ (%): C, 48.80; H, 4.64; N, 7.59. Found: C, 48.82; H, 4.70; N, 7.52.

4.3.27. *4-Ethyl 7-methyl 8-iodo-6-isopropylpyrrolo[1,2-a]pyrazine-4,7-dicarboxylate (8f)*. Yield: 52%, yellow-orange solid, mp 79-80 °C. IR spectrum, ν , cm^{-1} : 1715 (C=O). 1H -NMR (400 MHz, $CDCl_3$), δ , ppm: 1.39-1.46 (9H, m, OCH_2CH_3 + $CH(CH_3)_2$), 3.11-3.21 (1H, m, $CH(CH_3)_2$), 3.98 (3H, s, OCH_3), 4.47 (2H, k, J = 7.2 Hz, OCH_2CH_3), 7.98 (1H, s, H-3), 8.81 (1H, s, H-1). ^{13}C -NMR (100.6 MHz, $CDCl_3$), δ , ppm: 14.1, 20.6 (2C), 28.3, 52.2, 62.7, 64.4, 121.7, 124.4, 128.8, 134.6, 139.7, 150.1, 162.9, 165.1. MS, m/z (I_{rel} , %): 417 $[M+H]^+$ (100). Anal. Calcd. for $C_{15}H_{17}IN_2O_4$ (%): C, 43.29; H, 4.12; N, 6.73. Found: C, 43.20; H, 4.15; N, 6.70.

4.3.28. *Diethyl 8-bromo-6-phenylpyrrolo[1,2-a]pyrazine-4,7-dicarboxylate (8g)*. Yield: 57%, greenish yellow solid, mp 127-128 °C. IR spectrum, ν , cm^{-1} : 1721 (C=O). 1H -NMR (400 MHz, $CDCl_3$), δ , ppm: 1.08 (3H, t, J = 7.2 Hz, OCH_2CH_3), 1.16 (3H, t, J = 7.2 Hz, OCH_2CH_3), 3.65 (2H, k, J = 7.2 Hz, OCH_2CH_3), 4.24 (2H, k, J = 7.2 Hz, OCH_2CH_3), 7.36-7.44 (2H, m, Ar-H), 7.45-7.49 (3H, m, Ar-H), 7.92 (1H, s, H-3), 9.01 (1H, s, H-1). ^{13}C -NMR (100.6 MHz, $CDCl_3$), δ , ppm: 13.8, 13.9, 61.2, 62.2, 96.7, 120.8, 121.8, 126.8, 128.5 (2C), 129.0 (2C), 129.3, 130.8, 131.8, 133.5, 147.9, 161.3, 162.8. MS, m/z (I_{rel} , %): 417 $[M+H]^+$ (100). Anal. Calcd. for $C_{19}H_{17}BrN_2O_4$ (%): C, 54.69; H, 4.11; N, 6.71. Found: C, 54.77; H, 4.02; N, 6.59.

4.3.29. *4-Ethyl 7-methyl 8-bromo-6-(4-methoxyphenyl)pyrrolo[1,2-a]pyrazine-4,7-dicarboxylate (8h)*. Yield: 55%, greenish yellow solid, mp 128-129 °C. IR spectrum, ν , cm^{-1} : 1724 (C=O). 1H -NMR (400 MHz, $CDCl_3$), δ , ppm: 1.08 (3H,

t, $J = 7.2$ Hz, OCH_2CH_3), 3.69 (2H, k, $J = 7.2$ Hz, OCH_2CH_3), 3.75 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 6.95 (2H, d, $J = 8.8$ Hz, Ar-H), 7.26 (2H, d, $J = 8.8$ Hz, Ar-H), 7.86 (1H, s, H-3), 8.94 (1H, s, H-1). ^{13}C -NMR (125.6 MHz, CDCl_3), δ , ppm: 13.8, 51.9, 55.4, 62.3, 96.4, 113.9 (2C), 120.3, 121.9, 122.8, 126.8, 130.4 (2C), 131.9, 133.5, 148.0, 160.3, 161.4, 163.4. MS, m/z (I_{rel} , %): 433 $[\text{M}+\text{H}]^+$ (100). Anal. Calcd. for $\text{C}_{19}\text{H}_{17}\text{BrN}_2\text{O}_5$ (%): C, 52.67; H, 3.95; N, 6.47. Found: C, 52.59; H, 3.90; N, 6.46.

4.3.30. 4-Ethyl 7-methyl 8-chloro-6-(4-fluorophenyl)pyrrolo[1,2-a]pyrazine-4,7-dicarboxylate (**8i**). Yield: 52%, greenish yellow solid, mp 136-138 °C. IR spectrum, ν , cm^{-1} : 1720 (C=O). ^1H -NMR (400 MHz, CDCl_3), δ , ppm: 1.11 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 3.72-3.77 (5H, m, $\text{OCH}_3 + \text{OCH}_2\text{CH}_3$), 7.11-7.15 (2H, m, Ar-H), 7.31-7.34 (2H, m, Ar-H), 7.89 (1H, s, H-3), 9.00 (1H, s, H-1). ^{13}C -NMR (125.6 MHz, CDCl_3), δ , ppm: 13.3, 51.4, 61.8, 110.8, 115.1 (2C, d, $^2J_{\text{CF}} = 21.4$ Hz), 118.0, 120.9, 125.0, 126.2 (d, $^4J_{\text{CF}} = 3.8$ Hz), 129.6, 130.6 (2C, d, $^3J_{\text{CF}} = 8.8$ Hz), 133.4, 146.7, 160.6 (CO_2Alk), 162.4 (CO_2Alk), 162.6 (d, $^1J_{\text{CF}} = 251.2$ Hz). MS, m/z (I_{rel} , %): 377 $[\text{M}+\text{H}]^+$ (100). Anal. Calcd. for $\text{C}_{18}\text{H}_{14}\text{ClFN}_2\text{O}_4$ (%): C, 57.38; H, 3.75; N, 7.44. Found: C, 57.45; H, 3.75; N, 7.42.

4.3.31. 4-Ethyl 7-methyl 8-bromo-6-(4-fluorophenyl)pyrrolo[1,2-a]pyrazine-4,7-dicarboxylate (**8j**). Yield: 73%, greenish yellow solid, mp 156-158 °C. IR spectrum, ν , cm^{-1} : 1719 (C=O). ^1H -NMR (400 MHz, CDCl_3), δ , ppm: 1.10 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 3.71-3.77 (5H, m, $\text{OCH}_3 + \text{OCH}_2\text{CH}_3$), 7.11-7.15 (2H, m, Ar-H), 7.30-7.33 (2H, m, Ar-H), 7.90 (1H, s, H-3), 8.97 (1H, s, H-1). ^{13}C -NMR (125.6 MHz, CDCl_3), δ , ppm: 13.3, 51.4, 61.8, 95.7, 115.1 (2C, d, $^2J_{\text{CF}} = 22.6$ Hz), 119.8, 121.0, 126.3 (d, $^4J_{\text{CF}} = 3.8$ Hz), 126.4, 130.2, 130.6 (2C, d, $^3J_{\text{CF}} = 7.5$ Hz), 133.6, 147.8, 160.7 (CO_2Alk), 162.6 (d, $^1J_{\text{CF}} = 249.9$ Hz), 162.7 (CO_2Alk). MS, m/z (I_{rel} , %): 423 $[\text{M}+\text{H}]^+$ (100). Anal. Calcd. for $\text{C}_{18}\text{H}_{14}\text{BrFN}_2\text{O}_4$ (%): C, 51.33; H, 3.35; N, 6.65. Found: C, 51.39; H, 3.30; N, 6.61.

4.3.32. 4-Ethyl 7-methyl 6-(4-fluorophenyl)-8-iodopyrrolo[1,2-a]pyrazine-4,7-dicarboxylate (**8k**). IR spectrum, ν , cm^{-1} : 1722 (C=O). Yield: 53%, yellow-orange solid, mp 158-160 °C. ^1H -NMR (400 MHz, CDCl_3), δ , ppm: 1.10 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 3.71-3.76 (5H, m, $\text{OCH}_3 + \text{OCH}_2\text{CH}_3$), 7.11-7.15 (2H, m, Ar-H), 7.29-7.33 (2H, m, Ar-H), 7.91 (1H, s, H-3), 8.92 (1H, s, H-1). ^{13}C -NMR (125.6 MHz, CDCl_3), δ , ppm: 13.3, 51.3, 61.8, 62.9, 115.1 (2C, d, $^2J_{\text{CF}} = 21.6$ Hz), 121.5, 123.2, 126.5 (d, $^4J_{\text{CF}} = 3.8$ Hz), 129.2, 130.6 (2C, d, $^3J_{\text{CF}} = 8.8$ Hz), 131.3, 133.5, 149.6, 160.5 (CO_2Alk), 162.6 (d, $^1J_{\text{CF}} = 251.2$ Hz), 162.9 (CO_2Alk). MS, m/z (I_{rel} , %): 469 $[\text{M}+\text{H}]^+$ (100). Anal. Calcd. for $\text{C}_{18}\text{H}_{14}\text{IFN}_2\text{O}_4$ (%): C, 46.17; H, 3.01; N, 5.98. Found: C, 46.17; H, 3.07; N, 5.99.

4.3.33. 8-Iodo-6-isopropyl-7-(methoxycarbonyl)pyrrolo[1,2-a]pyrazine-4-carboxylic acid (**9**). Yield: 77%, green solid, mp 156-158 °C. IR spectrum, ν , cm^{-1} : 1714, 1739 (C=O), 2377-2759 (COOH), 3423 (OH). ^1H -NMR (400 MHz, DMSO-d_6), δ , ppm: 1.28 (3H, d, $J = 7.2$ Hz, $\text{CH}(\text{CH}_3)_2$), 3.22-3.32 (1H, m, $\text{CH}(\text{CH}_3)_2$), 3.90 (3H, s, OCH_3), 7.99 (1H, s, H-3), 8.78 (1H, s, H-1). The protons of the COOH group are in exchange with the water molecules of the DMSO-d_6 . ^{13}C -NMR (100.6 MHz, DMSO-d_6) δ (ppm): 21.0 (2C), 27.9, 52.8, 66.0, 123.1, 124.9, 128.7, 133.1, 138.5, 149.2, 164.4, 165.7. MS, m/z (I_{rel} , %): 389 $[\text{M}+\text{H}]^+$ (100). Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{IN}_2\text{O}_4$ (%): C, 40.23; H, 3.38; N, 7.22. Found C, 40.29; H, 3.31; N, 7.27.

4.3.34. 8-Bromo-6-methylpyrrolo[1,2-a]pyrazine-4,7-dicarboxylic acid (**10a**). Yield: 80%, brown solid, mp >250 °C. IR spectrum, ν , cm^{-1} : 1717 (C=O), 2386-2724 (COOH), 3423 (OH). ^1H -NMR (400 MHz, DMSO-d_6), δ , ppm: 2.59 (3H, s, CH_3), 8.12 (1H, s, H-3), 9.06 (1H, s, H-1). The protons of the COOH group are in exchange with the water molecules of the DMSO-d_6 . ^{13}C -NMR (100.6 MHz, DMSO-d_6), δ , ppm: 14.9, 98.8, 121.4, 122.9, 126.7, 130.8, 133.1, 145.9, 162.8, 164.5. MS, m/z (I_{rel} , %): 299 $[\text{M}+\text{H}]^+$ (100). Anal. Calcd. for $\text{C}_{10}\text{H}_7\text{BrN}_2\text{O}_4$ (%): C, 40.16; H, 2.36; N, 9.37. Found: C, 40.23; H, 2.40; N, 9.42.

4.3.35. 8-Iodo-6-isopropylpyrrolo[1,2-a]pyrazine-4,7-dicarboxylic acid (**10b**). Yield: 70%, green solid, mp 182-185 °C (decomposition). IR spectrum, ν , cm^{-1} : 1714 (C=O), 2395-2742 (COOH), 3432 (OH). ^1H -NMR (400 MHz, DMSO-d_6), δ , ppm: 1.30 (6H, d, $J = 7.2$ Hz, $\text{CH}(\text{CH}_3)_2$), 3.19-3.29 (1H, m, $\text{CH}(\text{CH}_3)_2$), 7.91 (1H, s, H-3), 8.70 (1H, s, H-1). The protons of the COOH group are in exchange with the water molecules of the DMSO-d_6 . ^{13}C -NMR (125.6 MHz, DMSO-d_6), δ , ppm: 20.9 (2C), 27.9, 65.4, 123.3, 126.5, 128.5, 132.9, 137.6, 148.9, 164.5, 166.9. MS, m/z (I_{rel} , %): 375 $[\text{M}+\text{H}]^+$ (100). Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{IN}_2\text{O}_4$ (%): C, 38.52; H, 2.96; N, 7.49. Found: C, 38.33; H, 3.04; N, 7.61.

4.3.36. 8-Bromo-6-phenylpyrrolo[1,2-a]pyrazine-4,7-dicarboxylic acid (**10c**). Yield: 84%, green solid, mp 210-212 °C. IR spectrum, ν , cm^{-1} : 1718 (C=O), 2405-2753 (COOH), 3438 (OH). ^1H -NMR (400 MHz, DMSO-d_6), δ , ppm: 7.33-7.41 (5H, m, Ar-H), 7.97 (1H, s, H-3), 8.99 (1H, s, H-1). The protons of the COOH group are in exchange with the water molecules of the DMSO-d_6 . ^{13}C -NMR (100.6 MHz, DMSO-d_6), δ , ppm: 94.8, 122.2, 122.6, 126.7, 128.7 (2C), 129.0 (2C), 129.3, 131.0, 131.3, 133.5, 147.6, 162.4, 164.6. MS, m/z (I_{rel} , %): 361 $[\text{M}+\text{H}]^+$ (100). Anal. Calcd. for $\text{C}_{15}\text{H}_9\text{BrN}_2\text{O}_4$ (%): C, 49.89; H, 2.51; N, 7.76. Found: C, 49.72; H, 2.55; N, 7.64.

4.3.37. 8-Chloro-6-(4-fluorophenyl)pyrrolo[1,2-a]pyrazine-4,7-dicarboxylic acid (**10d**). Yield: 82%, green solid, mp 218-220 °C. IR spectrum, ν , cm^{-1} : 1715 (C=O), 2415-2748 (COOH), 3427 (OH). ^1H -NMR (400 MHz, DMSO-d_6), δ , ppm: 7.20-7.24 (2H, m, Ar-H), 7.36-7.40 (2H, m, Ar-H), 7.91 (1H, s, H-3), 9.02 (1H, s, H-1). The protons of the COOH group are in exchange with the water molecules of the DMSO-d_6 . ^{13}C -NMR (125.6 MHz, DMSO-d_6), δ , ppm: 109.1, 115.6 (2C, d, $^2J_{\text{CF}} = 21.4$ Hz), 119.6, 122.5, 125.4, 127.7 (d, $^4J_{\text{CF}} = 2.5$ Hz), 129.6, 131.9 (2C, d, $^3J_{\text{CF}} = 8.8$ Hz), 133.5, 146.8, 162.5, 162.8 (d,

$^1J_{CF} = 244.9$ Hz), 163.9. MS, m/z (I_{rel} , %): 335 $[M+H]^+$ (100). Anal. Calcd. for $C_{15}H_8ClFN_2O_4$ (%): C, 53.83; H, 2.41; N, 8.37. Found: C, 53.89; H, 2.49; N, 8.39.

4.3.38. 4-Ethyl 7-methyl 8-bromo-6-(4-fluorophenyl)pyrrolo[1,2-a]pyrazine-4,7-dicarboxylic acid (**10e**). Yield: 81%, green solid, mp 205-207 °C. IR spectrum, ν , cm^{-1} : 1713 (C=O), 2410-2750 (COOH), 3430 (OH). 1H -NMR (400 MHz, DMSO- d_6), δ , ppm: 7.23-7.28 (2H, m, Ar-H), 7.39-7.43 (2H, m, Ar-H), 7.96 (1H, s, H-3), 8.99 (1H, s, H-1). The protons of the COOH group are in exchange with the water molecules of the DMSO- d_6 . ^{13}C -NMR (100.6 MHz, DMSO- d_6), δ , ppm: 95.0, 115.6 (2C, d, $^2J_{CF} = 21.1$ Hz), 121.7, 122.6, 126.7, 127.8 (d, $^4J_{CF} = 2.0$ Hz), 130.2, 131.7 (2C, d, $^3J_{CF} = 9.1$ Hz), 133.5, 147.6, 162.5, 162.8 (d, $^1J_{CF} = 239.4$ Hz), 164.3. MS, m/z (I_{rel} , %): 379 $[M+H]^+$ (100). Anal. Calcd. for $C_{15}H_8BrFN_2O_4$ (%): C, 47.52; H, 2.13; N, 7.39. Found: C, 47.59; H, 2.19; N, 7.33.

4.3.39. Dimethyl 6-methyl-8-phenylpyrrolo[1,2-a]pyrazine-4,7-dicarboxylate (**11a**). Yield: 35%, greenish yellow solid, mp 109-110 °C. IR spectrum, ν , cm^{-1} : 1739 (C=O). 1H -NMR (400 MHz, $CDCl_3$), δ , ppm: 2.61 (1H, s, CH_3), 3.69 (1H, s, OCH_3), 4.01 (1H, s, OCH_3), 7.37-7.45 (5H, m, Ar-H), 8.07 (1H, s, H-3), 8.69 (1H, s, H-1). ^{13}C -NMR (100.6 MHz, $CDCl_3$), δ , ppm: 14.3, 51.6, 53.0, 118.8, 120.2, 124.5, 127.0, 127.8, 128.1 (2C), 130.4 (2C), 130.9, 132.3, 135.2, 148.9, 162.7, 165.5. MS, m/z (I_{rel} , %): 325 $[M+H]^+$ (100). Anal. Calcd. for $C_{18}H_{16}N_2O_4$ (%): C, 66.66; H, 4.97; N, 8.64. Found: C, 66.69; H, 5.00; N, 8.65.

4.3.40. Dimethyl 6-isopropyl-8-(4-nitrophenyl)pyrrolo[1,2-a]pyrazine-4,7-dicarboxylate (**11b**). Yield: 34%, greenish yellow solid, mp 152-153 °C. IR spectrum, ν , cm^{-1} : 1743 (C=O). 1H -NMR (400 MHz, $CDCl_3$), δ , (ppm): 1.41-1.45 (9H, m, $OCH_2CH_3 + CH(CH_3)_2$), 3.16-3.27 (1H, m, $CH(CH_3)_2$), 3.70 (3H, s, OCH_3), 4.47 (2H, k, $J = 7.2$ Hz, OCH_2CH_3), 7.56 (2H, d, $J = 8.8$ Hz, Ar-H), 7.97 (1H, s, H-3), 8.30 (2H, d, $J = 8.8$ Hz, Ar-H), 8.69 (1H, s, H-1). ^{13}C -NMR (125.6 MHz, $CDCl_3$), δ , ppm: 14.1, 20.6 (2C), 28.0, 52.1, 62.7, 119.8, 121.1, 121.6, 123.7 (2C), 125.9, 130.6 (2C), 134.7, 138.2, 139.5, 147.3, 147.8, 163.2, 166.0. MS, m/z (I_{rel} , %): 412 $[M+H]^+$ (100). Anal. Calcd. for $C_{21}H_{21}N_3O_6$ (%): C, 61.31; H, 5.14; N, 10.21. Found: C, 60.98; H, 4.99; N, 10.34.

4.3.41. Dimethyl 6-isopropyl-8-(4-(trifluoromethyl)phenyl)pyrrolo[1,2-a]pyrazine-4,7-dicarboxylate (**11c**). Yield: 60%, greenish yellow solid, mp 108-109 °C. IR spectrum, ν , cm^{-1} : 1743 (C=O). 1H -NMR (400 MHz, $CDCl_3$), δ , ppm: 1.41-1.45 (9H, m, $OCH_2CH_3 + CH(CH_3)_2$), 3.17-3.28 (1H, m, $CH(CH_3)_2$), 3.69 (3H, s, OCH_3), 4.46 (2H, k, $J = 7.2$ Hz, OCH_2CH_3), 7.51 (2H, d, $J = 8.0$ Hz, Ar-H), 7.68 (2H, d, $J = 8.0$ Hz, Ar-H), 7.96 (1H, s, H-3), 8.68 (1H, s, H-1). ^{13}C -NMR (125.6 MHz, $CDCl_3$), δ , ppm: 14.1, 20.6 (2C), 28.0, 52.0, 62.6, 119.9, 121.4, 122.1, 124.2 (k, $^1J_{CF} = 272.6$ Hz), 125.4 (2C, k, $^3J_{CF} = 3.8$ Hz), 126.0, 129.8 (k, $^2J_{CF} = 32.7$ Hz), 130.2 (2C), 134.6, 136.2, 137.8, 148.1, 163.3, 166.3. MS, m/z (I_{rel} , %): 435 $[M+H]^+$ (100). Anal. Calcd. for $C_{22}H_{21}F_3N_2O_4$ (%): C, 60.83; H, 4.87; N, 6.45. Found: C, 60.68; H, 4.92; N, 6.52.

4.3.42. 4-Ethyl 7-methyl 6-isopropyl-8-(phenylethynyl)pyrrolo[1,2-a]pyrazine-4,7-dicarboxylate (**12**). Yield: 67%. Greenish yellow solid, m. p. 112-113 °C; 1H -NMR (400 MHz, $CDCl_3$) δ (ppm): 1.39-1.44 (9H, m, $OCH_2CH_3 + CH(CH_3)_2$), 3.06-3.16 (1H, m, $CH(CH_3)_2$), 3.97 (3H, s, OCH_3), 4.44 (2H, k, $J = 7.2$ Hz, OCH_2CH_3), 7.33-7.37 (3H, m, Ar-H), 7.53-7.55 (2H, m, Ar-H), 7.97 (1H, s, H-3), 9.03 (1H, s, H-1); ^{13}C -NMR (125.6 MHz, $CDCl_3$) δ (ppm): 14.1, 20.1 (2C), 28.3, 52.0, 62.6, 80.4, 96.2, 105.0, 121.2, 121.7, 123.3, 128.4, 128.5 (2C), 129.7, 131.6 (2C), 135.4, 139.6, 148.6, 163.2, 164.7. MS, m/z (I_{rel} , %): 391 $[M+H]^+$ (100). Anal. Calcd. for $C_{23}H_{22}N_2O_4$ (%): C, 70.75; H, 5.68; N, 7.17. Found: C, 70.55; H, 5.55; N, 7.07.

4.4 Antimicrobial activity

Some archival test-strains of bacteria and fungi were used in the present research (*Staphylococcus aureus* ATCC 25923, *Bacillus subtilis* ATCC 6633, *Pseudomonas aeruginosa* ATCC 27853, *Klebsiella pneumoniae* ATCC 1388, *Candida albicans* ATCC 885/653 and *Aspergillus niger* K9). The antimicrobial activity of the synthesized compounds was investigated using the method of nutrient broth microdilution as recommended by EUCAST (European Committee on Antimicrobial Susceptibility Testing).³² According to this method, the minimal inhibitory concentration (MIC) was determined as the concentration of every synthesized compound required to suppress the proliferation of the given microbial culture in the multihole microplate. The stock 1000 $\mu g/mL$ solution was prepared by dissolving the required amount of a compound in dimethyl sulfoxide (DMSO). Further, diluted solutions with the concentrations from 500 to 3.9 $\mu g/mL$ (or from 500 to 0.48 $\mu g/mL$ in the case of control drugs) were used to find the MIC values. The sensitivity of every microbial culture to every concentration of the synthesized compounds was tested three times. Besides, the control experiments were carried out to check the proliferation of microbes in the clean broth, in the same broth with an admixture of DMSO, and in the broth with DMSO and the control drugs (Decasium³³ and Clotrimazole³⁴) (Table 1). The control clear broth remained sterile and transparent (no proliferation of the microbial cultures), while some proliferation of the cultures was registered in the case of a mixture of DMSO and the broth.

4.5. Molecular docking study

The crystal structure of Kinase ThiM from *Klebsiella pneumoniae* and DNA gyrase from *Staphylococcus aureus* were downloaded from the protein data bank (PDB 6k28 and 5cdp, respectively), the water molecules and heteroatoms were removed, the polar hydrogen atoms were added, and the Gasteiger charges were applied to the protein's structure. The molecular docking study was performed using the software Autodock Vina1.2.7.³⁵ AutoDock Tools-1.5.7 was used to prepare the proteins and perform molecular docking³⁶. The centres of the ligand docking cavity of Kinase ThiM from *Klebsiella pneumoniae* (21.0; 62.4; 37.2) and DNA gyrase from *Staphylococcus aureus* (11.1; 50.9; 45.5) were determined using BIOVIA Discovery Studio Visualizer v21.1. The cavity dimensions were 20, 18, 16 for Kinase ThiM and 25, 25, 25 for DNA gyrase. The docking was visualized using BIOVIA Discovery Studio Visualizer v21.1. The Autodock Vina1.2.7 demonstrated sufficient accuracy in redocking of the original ligands, with root mean square deviation (RMSD) values of less than 2 Å (observed RMSD: 0.9720 Å for ligand 6k28 (TZE) and 0.7181 Å for ligand 5cdp (EVP)).

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