Synthesis, Reactions and Antibacterial Activity of 3-Acetyl[1,2,4]triazolo[3,4-*a*]isoquinoline Derivatives using Chitosan as Heterogeneous Catalyst under Microwave Irradiation

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3-Acetyl[1,2,4]triazolo[3,4-*a*]isoquinolines were prepared using chitosan as a catalyst. These compounds were used to prepare a novel series of enaminones **5**, and their reactions with hydrazonoyl halides **1** and **11** gave triazoloisoquinolines **8** and **13**, respectively, with a carbonylpyrazole side chain. Hydrazinolysis of **8** and **13** gave the pyrazolopyridazines **10** and pyrazolopyridazinones **14**. Reaction of **5** with hydroximoyl halides **15** led to triazoloisoquinoline **16** with a carbonylisoxazole side chain. Antibacterial effects of compounds **8** and **10** were studied.

Key words: [1,2,4]Triazolo[3,4-*a*]isoquinoline, Enaminones, Hydrazinolysis, Hydrazonoyl Chlorides, Cycloaddition Reaction, Chitosan, Hydroximoyl Chloride

Introduction

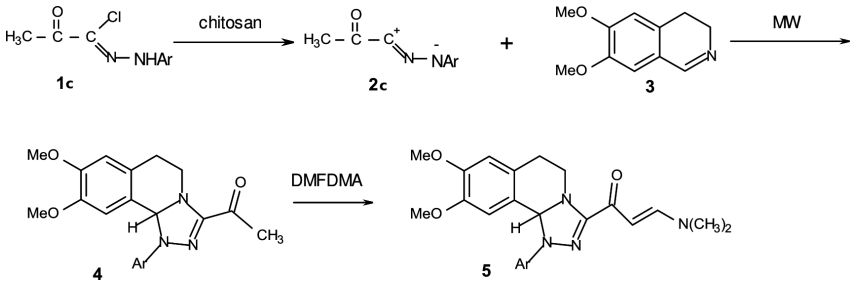
Fused isoquinoline derivatives are a very interesting class of compounds due to their significant pharmacological and biological activities [1 – 7]. As a part of our ongoing studies aimed at developing simple and efficient syntheses of polyfunctional heteroaromatic compounds from readily obtained starting materials, we have previously reported the syntheses of triazoloisoquinoline and pyrroloisoquinoline compounds *via* the reaction of 3,4-dihydro-6,7-dimethoxyisoquinoline derivatives with hydrazonoyl halides in chloroform in the presence of triethylamine or in pyridine as catalyst and solvent [8 – 16]. The aim of the present study has been to introduce a new synthetic methodology by (1) replacing triethylamine in chloroform by the ecologically more acceptable catalyst chitosan [17, 18], a naturally-occurring environmentally friendly polymer that can be used as a heterogeneous catalyst, thus affording a new environmentally benign route to the above compounds, and (2) carrying out the chitosan-catalyzed reactions under microwave irradiation to enhance reaction rates [19 – 26] for the synthesis of [1,2,4]triazolo[3,4-*a*]isoquinolines which were found to be useful precursors for the synthesis of enaminones **5**. The latter compounds **5** were used to prepare conjugates of triazoloisoquinolines with carbonylpyrazoles **8** and **13**, pyrazolopyridazines **10**, pyrazolopyridazinones **14**, and carbonylisoxazoles **16**. The antibacterial effects of compounds **8** and **10** were also examined.

Results and Discussion

The starting material, 3,4-dihydro-6,7-dimethoxyisoquinoline (**3**), was prepared *via* ring closure of *N*-[2-(3,4-dimethoxyphenyl)ethyl]formamide, prepared by heating equimolar amounts of formic acid and 2-(3,4-dimethoxyphenyl)ethylamine with $POCl_3$ in $CHCl_3$ according to the procedure of Bischler and Napieralsky [27].

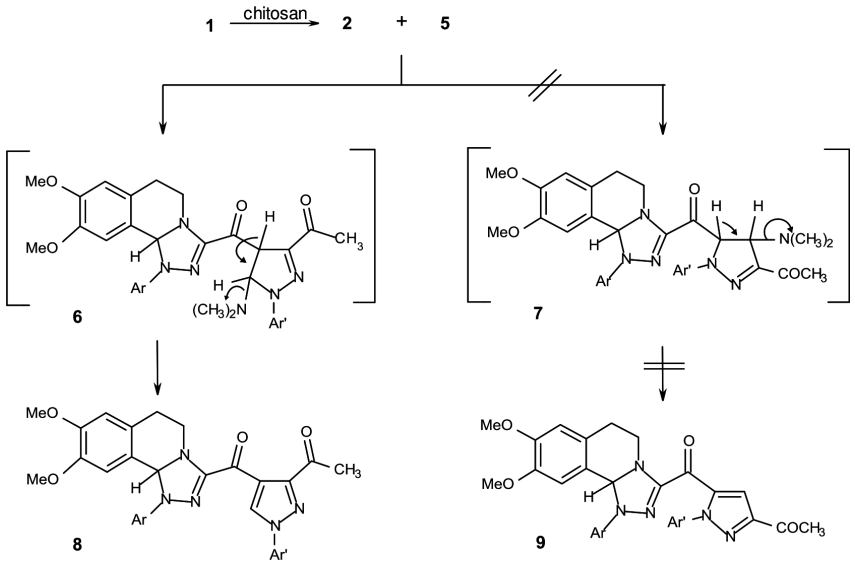
Reaction of **2c**, generated in *situ by* treatment of hydrazonoyl chloride **1c** with chitosan [28] in ethanol, with **3** under microwave irradiation for 10 min afforded a single product, as evidenced by TLC and ^{1}H NMR analysis of the crude product mixture. The purified product gave the correct elemental analysis and mass spectrum for the cycloadduct **4c** (Scheme 1).

As an example, the structure of **4c** was confirmed by NMR spectroscopy. The ^{1}H NMR spectrum revealed a signal at δ = 2.42 ppm assignable to the protons of the CH_3CO group, in addition to protons of the isoquinoline and aromatic groups. Its ^{13}C NMR spectrum afforded 18 signals, as expected. Similar reac-



1, 2, 4, 5	Ar
a	Ph
b	*p*-Tol
c	*p*-ClC_6H_4

Scheme 1. Synthesis of 3-acetyl[1,2,4]triazolo[3,4-*a*]isoquinolines **5**.



8	Ar / Ar′
a	Ph / Ph
b	Ph / *p*-Tol
c	Ph / *p*-ClC_6H_4
d	*p*-Tol / Ph
e	*p*-Tol / *p*-Tol
f	*p*-Tol / *p*-ClC_6H_4
g	*p*-ClC_6H_4 / Ph
h	*p*-ClC_6H_4 / *p*-Tol
i	*p*-ClC_6H_4 / *p*-ClC_6H_4

Scheme 2. Synthesis of pyrazoles **8**.

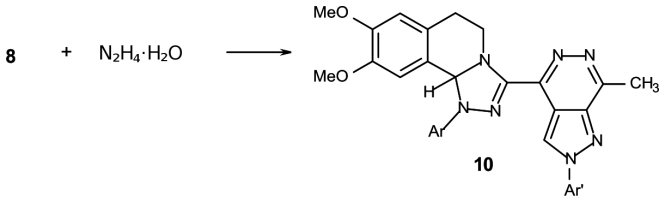
tions afforded **4a** and **4b**. The required enaminones **5**, which have not been reported hitherto, were prepared by refluxing **4** in dimethylformamide-dimethylacetal (DMFDMA) for 4 h. The structures of the enaminones were confirmed by their elemental analyses and spectral data (see Experimental Section). For example, the ^{1}H NMR spectrum of **5a** showed two singlets at δ = 2.87 and 3.08 ppm characteristic for the -NMe_2 group, two doublets at δ = 5.8 and 7.66 ppm with the coupling constant J = 13 Hz, assignable to the two olefinic protons. The value of the coupling constant is compatible with the (*E*)-configuration [29] depicted in Scheme 1.

Reaction of enaminones **5** with hydrazonoyl halides **1** in refluxing ethanol in the presence of chitosan gave, in each case, one isolable product as evidenced by TLC analysis (Scheme 2). Both elemental analyses and mass spectral data of the isolated products were consistent with either of two isomeric structures **8** or **9**. Structure **8** was assigned to the compounds based on careful analysis of the relevant ^{1}H NMR data.

The isomeric structure **9** was excluded as follows: For example, in the pyrazole ring system C-4 is the most electron rich carbon; thus, 4-H in **9** is expected to appear at high field of *ca.* δ = 6.31 ppm. On the other hand, 5-H in **8** is linked to the carbon atom attached to a nitrogen atom, and thus is deshielded and will appear in the region δ = 7.5 – 8.5 ppm [30 – 32]. The ^{1}H NMR spectra of the isolated reaction products revealed, in each case, a singlet at δ = 8.5 ppm which indicates the presence of the pyrazole 5-H rather than 4-H. The ^{13}C NMR spectra of all compounds were also in agreement with the proposed structures (see Experimental Section).

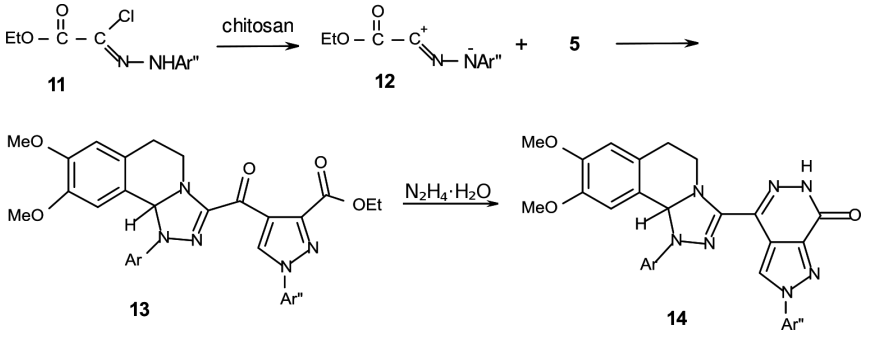
The proposed mechanism leading to the products starts with a regioselective 1,3-dipolar cycloaddition of nitrilimines **2** to the carbon-carbon double bond of the enaminones **5** to afford the cycloadducts **6** which affords the pyrazole derivatives **8** *via* elimination of dimethylamine.

In addition, the structure of compounds **8** was confirmed by their reactions with hydrazine hydrate. Thus,



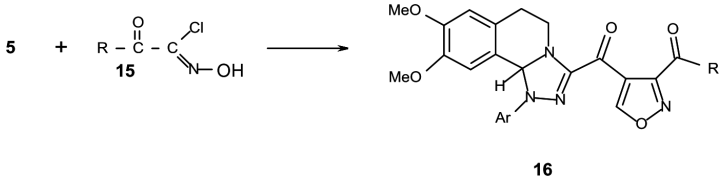
10	Ar / Ar′	10	Ar / Ar′
a	Ph / Ph	**g**	*p*-ClC_6H_4 / Ph
b	Ph / *p*-Tol	**h**	*p*-ClC_6H_4 / *p*-Tol
c	Ph / *p*-ClC_6H_4	**i**	*p*-ClC_6H_4 / *p*-ClC_6H_4
d	*p*-Tol / Ph		
e	*p*-Tol / *p*-Tol		
f	*p*-Tol / *p*-ClC_6H_4		

Scheme 3. Synthesis of pyrazolopyridazines **10**.



11, 12	Ar / Ar″
a	Ph / Ph
b	Ph / *p*-Tol
c	Ph / *p*-ClC_6H_4
d	*p*-Tol / Ph
e	*p*-Tol / *p*-Tol
f	*p*-Tol / *p*-ClC_6H_4
g	*p*-ClC_6H_4 / Ph
h	*p*-ClC_6H_4 / *p*-Tol
i	*p*-ClC_6H_4 / *p*-ClC_6H_4

Scheme 4. Synthesis of pyrazolopyridazinones **14**.



16	R / Ar	16	R / Ar
a	Ph / Ph	**d**	2-thienyl / Ph
b	Ph / *p*-Tol	**e**	2-thienyl / *p*-Tol
c	Ph / *p*-ClC_6H_4	**f**	2-thienyl / *p*-ClC_6H_4

R = Ph (**15b**) 2-thienyl (**15b**)

Scheme 5. Synthesis of isoxazoles **16**.

refluxing of **8** with hydrazine hydrate in ethanol afforded the pyrazolo[3,4-*d*]pyridazine derivatives **10** (Scheme 3). The structure of the products, suggested by their preparative route and elemental analyses, was further supported by their spectral properties. For example, the IR spectra revealed the absence of carbonyl bands. The ^{1}H NMR spectra yielded a signal for the pyridazine methyl group at δ = 2.95 ppm; the acetyl methyl signal in **8** occurred at δ = 2.27 ppm [33].

Next, hydrazonoyl chlorides **11** were treated with enaminones **5** in ethanol in the presence of chitosan to give the corresponding triazoloisoquinoline derivatives **13**. The structures of the products were established on the basis of elemental analyses and spectral data (IR, ^{1}H and ^{13}C NMR, mass spectra). For example, the ^{1}H NMR spectrum of **13a** revealed a singlet at δ = 8.5 ppm, assignable to the proton at position 5 of the pyrazole ring, a triplet at δ = 1.19 ppm and a quartet at δ = 4.30 ppm, assignable to the protons of ethoxycarbonyl group, in addition to the signals of the isoquinoline moiety and the aromatic rings. The structures of compounds **13** were further confirmed by their conversion to pyrazolopyridazinones **14** upon reaction with hydrazine hydrate (Scheme 4). The structures of the latter products **14** were confirmed on the basis of elemental and spectral analyses. The IR spectra of **14** showed bands at ν = 3159 and 1693 cm^{-1}, corresponding to NH and amide carbonyl groups, respectively, instead of the two carbonyl bands at ν = 1742 and 1641 cm^{-1} of **13**.

Stirring of equimolar amounts of enaminones **5** and hydroximoyl chloride **15** in acetonitrile at r. t. gave, in each case, one isolable product **16** (Scheme 5). The structures of the products were established from their elemental analyses and spectral data. For example, compound **16a** exhibits a molecular ion peak at m/z = 508 in its mass spectrum. Its IR spectrum showed two carbonyl bands at ν = 1693 and 1647 cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra confirmed the structure of the cycloadduct **16a** (see Experimental Section).

Biological screening

Eighteen compounds (**8a**–**i** and **10a**–**i**) were assayed for their antibacterial activities. It is clear from the data in Table 1 that compounds with an unsubstituted phenyl group in the triazoline moiety showed no antibacterial activities against the four pathogenic

Table 1. Antibacterial activity of compounds **8a – i** and **10a – i** using disc diffusion plates[a].

Compound	*Bacillus subtilis* (G^+)		*Escherichia coli* (G^-)		*Neisseria gonorrhoeae* (G^-)		*Staphylococcus aureus* (G^+)	
	I. Z. ($mm\,mg^{-1}$)	R. A. (%)	I. Z. ($mm\,mg^{-1}$)	R. A. (%)	I. Z. ($mm\,mg^{-1}$)	R. A. (%)	I. Z. ($mm\,mg^{-1}$)	R. A. (%)
Tetracycline (Standard)	32	100	30	100	29	100	28	100
8a	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
8b	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
8c	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
8d	12	37.5	14	46.7	10	34.5	11	39.3
8e	16	50.0	15	50.0	15	51.7	15	53.6
8f	12	37.5	12	40.0	11	37.9	13	46.4
8g	0.0	0.0	0.0	0.0	10	34.5	0.0	0.0
8h	11	34.4	12	40.0	13	44.9	14	50.0
8i	10	31.3	10	33.3	0.0	0.0	11	39.3
10a	13	40.6	11	36.7	12	41.4	12	42.9
10b	0.0	0.0	10	33.3	10	34.5	11	39.3
10c	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
10d	15	46.9	15	50.0	16	55.2	15	53.6
10e	11	34.4	12	40.0	11	37.9	12	42.9
10f	10	31.3	10	33.3	0.0	0.0	11	39.3
10g	0.0	0.0	10	33.3	10	34.5	10	35.7
10h	10	31.3	0.0	0.0	0.0	0.0	11	39.3
10i	10	31.3	0.0	0.0	0.0	0.0	0.0	0.0

[a] G^+ = gram positive; G^- = gram negative; I. Z. = inhibition zone; R. A. = relative activity.

bacteria under test, irrespective of the substitution in the phenyl group in the pyrazole ring (**8a**, **8b** and **8c**), while compounds with phenyl groups substituted by chlorine or methyl groups in the triazoline ring (**8d** – **8i**) showed antibacterial activities. Compounds with methyl groups showed higher activities against bacteria (**8d**, **8e** and **8f**) than compounds with the chlorine atom (**8g**, **8h** and **8i**). The most efficient compound in series **8** was **8e** which has two *p*-tolyl groups at position 1 in both the triazoline and the pyrazole ring, with relative activities compared to tetracycline of 50.0, 50.0, 51.7, and 53.6 %, respectively, in the four bacteria examined. Most of the pyrazolopyridazine compounds **10** showed antibacterial activities against some of the pathogenic bacteria. Compound **10c**, for example, exerted no antibacterial activity, while **10a**, **10d** and **10e** exerted antibacterial activities against the four pathogenic bacteria examined. Compound **10d** was the most efficient one in series **10**, with a relative activity compared to tetracycline of 46.9, 50.0, 55.2, and 53.6 %, respectively (Tables 1 and 2).

Table 2. MIC values for two efficient antibacterial compounds[a].

Compound	Bacterial species	MIC value ($\mu g\,mL^{-1}$)
8e	*Bacillus subtilis*	200
10d	*Neisseria gonorrhoeae*	246

[a] MIC values were determined for the highly efficient antibacterial compounds using the most sensitive microorganisms.

Experimental Section

General

The melting points were determined on a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded as KBr pellets using an FTIR Bruker-Vector 22 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and [D_6]DMSO as solvents at 300 MHz on a Varian Gemini NMR spectrometer using TMS as internal standard. Chemical shifts are reported in δ units (ppm). Mass spectra were measured on a Shimadzu GMMS-QP-1000 EX mass spectrometer at 70 eV. Microwave-assisted reactions were run in a CEM Discover labmate™ microwave apparatus (300 W with CHEMDRIVER™ software). The elemental analyses were performed at the Microanalytical Center, Cairo University. Compounds **1a – c** [34], **11a**, **b** [35], **11c** [35, 36], **15a** [37] and **15b** [38] had been prepared previously.

*General procedure for the preparation of 1-aryl-3-acetyl-8,9-dimethoxy[1,2,4]triazolo[3,4-a]1,5,6,10b-tetrahydroisoquinolines (**4a – c**)*

To a solution of hydrazonoyl chloride **1** (1 mmol) and 3,4-dihydro-6,7-dimethoxyisoquinoline (**3**) (0.28 g, 1 mmol) in absolute ethanol (5 mL) was added chitosan (0.1 g) at r. t. The reaction mixture was irradiated under constant pressure (11.2 bar, 80 °C) for 10 min at a power of 300 W. The hot solution was filtered to remove the chitosan. After cooling, dilute HCl was added to the solution until it became acidic. The solid product was collected and crystallized from a suitable

solvent. The compounds prepared and their physical data are listed below.

*1-Phenyl-3-acetyl-8,9-dimethoxy[1,2,4]triazolo[3,4-a]-1,5,6,10b-tetrahydroisoquinoline (**4a**)*

Yellow crystals, m. p. 130 °C (lit. [15]: 130 °C), 70 % yield.

*1-(4-Methylphenyl)-3-acetyl-8,9-dimethoxy[1,2,4]triazolo-[3,4-a]1,5,6,10b-tetrahydroisoquinoline (**4b**)*

Yellow crystals, m. p. 135 °C, (lit. [15]: 135 °C), 70 % yield.

*1-(4-Chlorophenyl)-3-acetyl-8,9-dimethoxy[1,2,4]triazolo-[3,4-a]1,5,6,10b-tetrahydroisoquinoline (**4c**)*

Yellow crystals, m. p. 158 °C (acetonitrile), 73 % yield. – IR (KBr): ν = 1674 (C=O) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.42 (s, 3H), 2.75 (m, 1H), 2.82 (m, 1H), 3.60 (s, 3H), 3.82 (s, 3H), 3.87 (m, 2H), 6.41 (s, 1H), 6.60 (s, 1H), 6.65 (s, 1H), 7.10 – 7.25 (m, 4H). – ^{13}C NMR ($CDCl_3$): δ = 26.58, 27.84, 42.11, 55.86, 55.96, 77.92, 108.02, 111.26, 114.93, 125.42, 127.71, 127.92, 129.08, 143.12, 147.76, 148.79, 148.88, 190.01. – MS: m/z (%) = 387 (57) $[M+2]^+$, 386 (10) $[M+2–H]^+$, 385 (100) $[M]^+$. – Anal. for $C_{20}H_{20}ClN_3O_3$: calcd. C 62.26, H 5.22, N 10.89; found C 62.41, H 5.10, N 10.66.

*Preparation of (E)-1-(8,9-dimethoxy-1-aryl-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]-isoquinolin-3-yl)-3-(dimethylamino)propenones (**5a – c**)*

A mixture of a 1-aryl-3-acetyl-8,9-dimethoxy[1,2,4]triazolo[3,4-*a*]1,5,6,10b-tetrahydroisoquinoline **4** (5 mmol) and DMF-DMA (3 mL) was refluxed for 4 h. The solid that precipitated was collected and crystallized from a suitable solvent. The compounds prepared with their physical data are listed below.

*(E)-1-(8,9-Dimethoxy-1-phenyl-1,5,6,10b-tetrahydro-[1,2,4]triazolo[3,4-a]isoquinolin-3-yl)-3-(dimethylamino)-propenone (**5a**)*

Orange crystals, m. p. 158 °C (ethanol), 78 % yield. – IR (KBr): ν = 1641 (C=O) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.70 (m, 1H), 2.84 (m, 1H), 2.87 (s, 3H), 3.08 (s, 3H), 3.64 (s, 3H), 3.85 (s, 3H), 3.86 (m, 1H), 4.00 (m, 1H), 5.80 (d, J = 13 Hz, 1H), 6.34 (s, 1H), 6.64 (s, 1H), 6.75 (s, 1H), 6.87 – 7.31 (m, 5H), 7.66 (d, J = 13 Hz, 1H). – ^{13}C NMR ($CDCl_3$): δ = 28.04, 37.30, 42.08, 45.50, 55.85, 55.97, 77.85, 108.44, 111.09, 113.59, 119.82, 125.90, 127.92, 129.04, 129.09, 146.41, 147.69, 148.56, 151.35, 153.16, 178.87. – MS: m/z (%) = 406 (59) $[M]^+$, 405 (100). – Anal. for $C_{23}H_{26}N_4O_3$: calcd. C 67.96, H 6.45, N 13.78; found C 67.86, H 6.43, N 14.03.

*(E)-1-(8,9-Dimethoxy-1-(4-methylphenyl)-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]iso-quinolin-3-yl)-3-(dimethylamino)propenone (**5b**)*

Orange crystals, m. p. 158 °C (ethanol), 80 % yield. – IR (KBr): ν = 1635 (C=O) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.27 (s, 3H), 2.70 (m, 1H), 2.84 (m, 1H), 2.87 (s, 3H), 3.04 (s, 3H), 3.64 (s, 3H), 3.79 (m, 1H), 3.82 (s, 3H), 4.01 (m, 1H), 5.80 (d, J = 13 Hz, 1H), 6.29 (s, 1H), 6.62 (s, 1H), 6.73 (s, 1H), 7.08 – 7.21 (m, 4H), 7.68 (d, J = 13 Hz, 1H). – ^{13}C NMR ($CDCl_3$): δ = 20.53, 28.06, 37.32, 42.09, 45.51, 55.84, 55.95, 78.31, 108.58, 111.07, 114.01, 125.90, 127.99, 129.13, 129.29, 129.54, 144.37, 147.64, 148.50, 151.20, 152.95, 178.88. – MS: m/z (%) = 420 (30) $[M]^+$, 98 (100). – Anal. for $C_{24}H_{28}N_4O_3$: calcd. C 68.55, H 6.71, N 13.32; found C 68.31, H 7.02, N 13.64.

*(E)-1-(8,9-Dimethoxy-1-(4-chlorophenyl)-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]iso-quinolin-3-yl)-3-(dimethylamino)propenone (**5c**)*

Orange crystals, m. p. 180 °C (acetonitrile), 79 % yield. – IR (KBr): ν = 1643 (C=O) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.73 (m, 1H), 2.85 (m, 1H), 2.89 (s, 3H), 3.08 (s, 3H), 3.66 (s, 3H), 3.83 (s, 3H), 3.87 (m, 1H), 3.97 (m, 1H), 5.83 (d, J = 13 Hz, 1H), 6.27 (s, 1H), 6.64 (s, 1H), 6.67 (s, 1H),7.07 – 7.23 (m, 4H), 7.69 (d, J = 13 Hz, 1H). – ^{13}C NMR ($CDCl_3$): δ = 28.04, 37.41, 42.08, 45.49, 55.90, 55.98, 77.69, 108.11, 111.14, 114.39, 124.34, 127.87, 128.79, 128.90, 129.09, 145.07, 147.77, 148.68, 151.60, 153.25, 178.61. – MS: m/z (%) = 442 (20) $[M+2]^+$, 441 (40) $[M+2–H]^+$, 440 (94) $[M]^+$, 439 (89) $[M–H]^+$, 98 (100). – Anal. for $C_{23}H_{25}ClN_4O_3$: calcd. C 62.65, H 5.72, Cl 8.04, N 12.71; found C 62.41, H 5.51, Cl 8.30, N 12.63.

*Synthesis of 1-[4-(8,9-dimethoxy-1-aryl-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]isoquinoline-3-carbonyl)-1-aryl-1H-pyrazol-3-yl]ethanones (**8a – i**)*

To a solution of a hydrazonoyl chloride **1** (1 mmol) and an enaminone **5** (1 mmol) in absolute ethanol (5 mL) was added chitosan (0.1 g) at r. t. The reaction mixture was irradiated under constant pressure (11.2 bar, 80 °C) for 10 min at a power of 300 W. The hot solution was filtered to remove chitosan. After cooling, dilute HCl was added to the solution until it became acidic. The solid was collected and crystallized from a suitable solvent. The compounds prepared and their physical data are listed below.

*1-[4-(8,9-Dimethoxy-1-phenyl-1,5,6,10b-tetrahydro[1,2,4]-triazolo[3,4-a]isoquinoline-3-carbonyl)-1-phenyl-1H-pyrazol-3-yl]ethanone (**8a**)*

Orange crystals, m. p. 160 °C (ethanol), 80 % yield. – IR (KBr): ν = 1700 (C=O), 1646 (C=O) cm^{-1}. – ^{1}H NMR

($CDCl_3$): δ = 2.64 (s, 3H), 2.74 (m, 1H), 3.10 (m, 1H), 3.61 (s, 3H), 3.85 (m, 1H), 3.87 (s, 3H), 3.95 (m, 1H), 6.64 (s, 1H), 6.70 (s, 1H), 6.71 (s, 1H), 6.96 – 7.77 (m, 10H), 8.52 (s, 1H). – ^{13}C NMR ($CDCl_3$): δ = 27.98, 28.25, 42.12, 55.86, 55.95, 78.47, 108.56, 111.34, 114.75, 119.97, 121.18, 122.18, 127.69, 128.06, 128.37, 129.21, 129.66, 131.57, 139.02, 144.31, 147.61, 148.82, 149.68, 152.07, 177.26, 194.01. – MS: m/z (%) = 521 (33) $[M]^+$, 520 (77), 77 (100). – Anal. for $C_{30}H_{27}N_5O_4$: calcd. C 69.08, H 5.22, N 13.43; found C 69.24, H 5.43, N 13.64.

*1-[4-(8,9-Dimethoxy-1-phenyl-1,5,6,10b-tetrahydro-[1,2,4]triazolo[3,4-a]isoquinoline-3-carbonyl)-1-(4-methylphenyl)-1H-pyrazol-3-yl]ethanone (**8b**)*

Orange crystals, m. p. 175 °C (dimethyl formamide), 78 % yield. – IR (KBr): ν = 1702 (C=O), 1644 (C=O) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.41 (s, 3H), 2.63 (s, 3H), 2.74 (m, 1H), 3.10 (m, 1H), 3.60 (s, 3H), 3.85 (m, 1H), 3.87 (s, 3H), 4.20 (m, 1H), 6.63 (s, 1H), 6.69 (s, 1H), 6.71 (s, 1H), 6.95 – 7.64 (m, 9H), 8.47 (s, 1H). – ^{13}C NMR ($CDCl_3$): δ = 20.98, 27.95, 28.24, 42.08, 55.83, 55.93, 78.40, 108.54, 111.32, 114.69, 119.85, 121.11, 121.96, 127.70, 128.34, 129.18, 130.13, 131.51, 136.73, 138.12, 144.31, 147.58, 148.79, 149.67, 151.86, 177.27, 194.03. – MS: m/z (%) = 535 (58) $[M]^+$, 534 (100). – Anal. for $C_{31}H_{29}N_5O_4$: calcd. C 69.52, H 5.46, N 13.08; found C 69.80, H 5.64, N 13.31.

*1-[4-(8,9-Dimethoxy-1-phenyl-1,5,6,10b-tetrahydro-[1,2,4]triazolo[3,4-a]isoquinoline-3-carbonyl)-1-(4-chlorophenyl)-1H-pyrazol-3-yl]ethanone (**8c**)*

Orange crystals, m. p. 196 °C (acetonitrile), 75 % yield. – IR (KBr): ν = 1702 (C=O), 1645 (C=O) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.61 (s, 3H), 2.74 (m, 1H), 3.04 (m, 1H), 3.58 (s, 3H), 3.80 (m, 1H), 3.86 (s, 3H), 4.16 (m, 1H), 6.63 (s, 1H), 6.65 (s, 1H), 6.68 (s, 1H), 6.92 – 7.71 (m, 9H), 8.47 (s, 1H). – ^{13}C NMR ($CDCl_3$): δ = 27.91, 28.22, 42.07, 55.82, 55.92, 78.47, 108.53, 111.34, 114.77, 121.02, 121.24, 122.39, 127.56, 128.33, 129.20, 129.75, 131.33, 133.70, 137.47, 144.14, 147.57, 148.80, 149.58, 152.15, 177.03, 193.80. – MS: m/z (%) = 557 (18) $[M+2]^+$, 556 (42) $[M+2–H]^+$, 555 (53) $[M]^+$, 554 (100) $[M–H]^+$. – Anal. for $C_{30}H_{26}ClN_5O_4$: calcd. C 64.80, H 4.71, Cl 6.38, N 12.60; found C 64.60, H 4.52, Cl 6.21, N 12.44.

*1-[4-(8,9-Dimethoxy-1-(4-methylphenyl)-1,5,6,10b-tetra-hydro[1,2,4]triazolo[3,4-a]iso-quinoline-3-carbonyl)-1-phenyl-1H-pyrazol-3-yl]ethanone (**8d**)*

Orange crystals, m. p. 124 °C (ethanol), 80 % yield. – IR (KBr): ν = 1705 (C=O), 1639 (C=O) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.27 (s, 3H), 2.61 (s, 3H), 2.70 (m, 1H), 3.10 (m, 1H), 3.57 (s, 3H), 3.80 (m, 1H), 3.83 (s, 3H), 4.20 (m, 1H), 6.58 (s, 1H), 6.66 (s, 1H), 6.69 (s, 1H), 7.04 – 7.73 (m, 9H), 8.48 (s, 1H). – ^{13}C NMR ($CDCl_3$): δ = 20.55, 27.93, 28.17, 42.13, 55.84, 55.93, 78.98, 109.01, 111.53, 115.41, 119.85, 122.27, 127.55, 127.93, 128.58, 129.57, 129.66, 130.93, 131.40, 139.00, 141.96, 147.58, 148.85, 149.44, 152.02, 177.10, 193.91. – MS: m/z (%) = 535 (64) $[M]^+$, 534 (100). – Anal. for $C_{31}H_{29}N_5O_4$: calcd. C 69.52, H 5.46, N 13.08; found C 69.33, H 5.21, N 13.31.

*1-[4-(8,9-Dimethoxy-1-(4-methylphenyl)-1,5,6,10b-tetra-hydro[1,2,4]triazolo[3,4-a]iso-quinoline-3-carbonyl)-1-(4-methylphenyl)-1H-pyrazol-3-yl]ethanone (**8e**)*

Orange crystals, m. p. 158 °C (ethanol), 76 % yield. – IR (KBr): ν = 1701 (C=O), 1647 (C=O) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.30 (s, 3H), 2.41 (s, 3H), 2.63 (s, 3H), 2.70 (m, 1H), 3.10 (m, 1H), 3.61 (s, 3H), 3.8 (m, 1H), 3.87 (s, 3H), 4.20 (m, 1H), 6.60 (s, 1H), 6.68 (s, 1H), 6.70 (s, 1H), 7.08 – 7.63 (m, 8H), 8.46 (s, 1H). – ^{13}C NMR ($CDCl_3$): δ = 20.59, 20.98, 27.97, 28.24, 42.15, 55.82, 55.91, 78.98, 108.76, 111.31, 115.35, 119.85, 122.04, 127.53, 128.51, 129.67, 130.11, 130.93, 131.46, 136.75, 138.07, 142.02, 147.50, 148.74, 149.49, 151.83, 177.16, 194.07. – MS: m/z (%) = 549 (53) $[M]^+$, 548 (100). – Anal. for $C_{32}H_{31}N_5O_4$: calcd. C 69.93, H 5.69, N 12.74; found C 69.62, H 5.41, N 12.98.

*1-[4-(8,9-Dimethoxy-1-(4-methylphenyl)-1,5,6,10b-tetra-hydro[1,2,4]triazolo[3,4-a]iso-quinoline-3-carbonyl)-1-(4-chlorophenyl)-1H-pyrazol-3-yl]ethanone (**8f**)*

Orange crystals, m. p. 188 °C (ethanol), 77 % yield. – IR (KBr): ν = 1705 (C=O), 1647 (C=O) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.30 (s, 3H), 2.62 (s, 3H), 2.75 (m, 1H), 3.10 (m, 1H), 3.60 (s, 3H), 3.86 (m, 1H), 3.87 (s, 3H), 4.20 (m, 1H), 6.61 (s, 1H), 6.66 (s, 1H), 6.68 (s, 1H), 7.05 – 7.71 (m, 8H), 8.46 (s, 1H). – ^{13}C NMR ($CDCl_3$): δ = 20.60, 27.94, 28.24, 42.14, 55.81, 55.90, 79.07, 108.75, 111.32, 115.45, 121.02, 122.48, 127.38, 128.50, 129.70, 129.75, 131.12, 131.29, 133.70, 137.50, 141.85, 147.49, 148.76, 149.40, 152.15, 176.90, 193.87. – MS: m/z (%) = 571 (16) $[M+2]^+$, 570 (79) $[M+2–H]^+$, 569 (82) $[M]^+$, 568 (100) $[M–H]^+$. – Anal. for $C_{31}H_{28}ClN_5O_4$: calcd. C 65.32, H 4.95, Cl 6.22, N 12.29; found C 65.22, H 4.87, Cl 6.18, N 12.46.

*1-[4-(8,9-Dimethoxy-1-(4-chlorophenyl)-1,5,6,10b-tetra-hydro[1,2,4]triazolo[3,4-a]iso-quinoline-3-carbonyl)-1-phenyl-1H-pyrazol-3-yl]ethanone (**8g**)*

Orange crystals, m. p. 145 °C (ethanol), 76 % yield. – IR (KBr): ν = 1705 (C=O), 1647 (C=O) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.61 (s, 3H), 2.76 (m, 1H), 3.04 (m, 1H), 3.63 (s, 3H), 3.85 (s, 3H), 3.89 (m, 1H), 4.09 (m, 1H), 6.52 (s, 1H), 6.63 (s, 1H), 6.70 (s, 1H), 7.04 – 7.75 (m, 9H), 8.48

(s, 1H). – ^{13}C NMR ($CDCl_3$): δ = 27.97, 28.14, 42.08, 55.93, 55.95, 78.25, 108.24, 111.39, 115.38, 119.88, 122.08, 125.76, 127.51, 128.10, 128.27, 129.09, 129.65, 131.46, 138.89, 143.09, 147.69, 148.92, 149.99, 151.98, 177.35, 193.87. – MS: m/z (%) = 557 (14) $[M+2]^+$, 556 (45) $[M+2–H]^+$, 555 (39) $[M]^+$, 554 (71) $[M–H]^+$, 287 (100). – Anal. for $C_{30}H_{26}ClN_5O_4$: calcd. C 64.80, H 4.71, Cl 6.38, N 12.60; found C 65.05, H 5.01, Cl 6.21, N 12.96.

*1-[4-(8,9-Dimethoxy-1-(4-chlorophenyl)-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]iso-quinoline-3-carbonyl)-1-(4-methylphenyl)-1H-pyrazol-3-yl]ethanone (**8h**)*

Orange crystals, m. p. 192 °C (acetonitrile), 80 % yield. – IR (KBr): ν = 1701 (C=O), 1651 (C=O) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.41 (s, 3H), 2.61 (s, 3H), 2.76 (m, 1H), 3.06 (m, 1H), 3.65 (s, 3H), 3.85 (m, 1H), 3.87 (s, 3H), 4.10 (m, 1H), 6.53 (s, 1H), 6.64 (s, 1H), 6.71 (s, 1H), 7.05 – 7.63 (m, 8H), 8.44 (s, 1H). – ^{13}C NMR ($CDCl_3$): δ = 20.97, 27.97, 28.12, 42.06, 55.91, 55.93, 78.22, 108.22, 111.35, 115.34, 119.81, 121.88, 125.71, 127.53, 128.24, 129.07, 130.12, 131.39, 136.64, 138.18, 143.13, 147.67, 148.89, 149.99, 151.81, 177.37, 193.88. – MS: m/z (%) = 571 (24) $[M+2]^+$, 570 (46) $[M+2–H]^+$, 569 (78) $[M]^+$, 568 (100) $[M–H]^+$, 227 (80). – Anal. for $C_{31}H_{28}ClN_5O_4$: calcd. C 65.32, H 4.95, Cl 6.22, N 12.29; found C 65.22, H 4.61, Cl 6.13, N 12.14.

*1-[4-(8,9-Dimethoxy-1-(4-chlorophenyl)-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]iso-quinoline-3-carbonyl)-1-(4-chlorophenyl)-1H-pyrazol-3-yl]ethanone (**8i**)*

Orange crystals, m. p. 200 °C (acetonitrile), 79 % yield. – IR (KBr): ν = 1705 (C=O), 1651 (C=O) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.61 (s, 3H), 2.76 (m, 1H), 3.04 (m, 1H), 3.64 (s, 3H), 3.84 (m, 1H), 3.87 (s, 3H), 4.07 (m, 1H), 6.53 (s, 1H), 6.62 (s, 1H), 6.70 (s, 1H), 7.04 – 7.71 (m, 8H), 8.45 (s, 1H). – ^{13}C NMR ($CDCl_3$): δ = 27.94, 28.14, 42.05, 55.88, 55.92, 78.27, 108.07, 111.26, 115.36, 120.99, 122.28, 125.83, 127.37, 128.19, 129.10, 129.77, 131.27, 133.79, 137.36, 142.96, 147.61, 148.85, 149.91, 152.08, 177.14, 193.74. – MS: m/z (%) = 593 (3) $[M+4]^+$, 592 (25) $[M+4–H]^+$, 591 (28) $[M+2]^+$, 590 (74) $[M+2–H]^+$, 589 (72) $[M]^+$, 588 (100) $[M–H]^+$, 587 (96). – Anal. for $C_{30}H_{25}Cl_2N_5O_4$: calcd. C 61.02, H 4.27, Cl 12.01, N 11.86; found C 61.31, H 4.48, Cl 11.81, N 11.91.

*Synthesis of 8,9-dimethoxy-3-(7-methyl-2-phenyl-2H-pyrazolo[3,4-d]pyridazin-4-yl)-1-phenyl-1,5,6,10b-tetrahydro-[1,2,4]triazolo[3,4-a]isoquinolines (**10a – i**)*

A 3-acetyl-4-carbonylpyrazole derivative **8** (5 mmol) in ethanol (30 mL) and hydrazine hydrate 99 % (0.7 mL, 10 mmol) were refluxed for 4 h, during which time the corresponding pyrazolopyridazine **10** precipitated. The solid was collected, washed with water, and crystallized from dimethyl formamide. The compounds prepared and their physical data are listed below.

*8,9-Dimethoxy-3-(7-methyl-2-phenyl-2H-pyrazolo[3,4-d]-pyridazin-4-yl)-1-phenyl-1,5,6,10b-tetra-hydro[1,2,4]triazolo[3,4-a]isoquinoline (**10a**)*

Red crystals, m. p. 230 °C, 89 % yield. – IR (KBr): no C=O bands. – ^{1}H NMR (DMSO): δ = 2.64 (s, 3H), 2.74 (m, 1H), 3.10 (m, 1H), 3.61 (s, 3H), 3.85 (m, 1H), 3.87 (s, 3H), 3.95 (m, 1H), 6.64 (s, 1H), 6.70 (s, 1H), 6.71 (s, 1H), 6.96 – 7.77 (m, 10H), 8.52 (s, 1H). – ^{13}C NMR (DMSO): δ = 18.09, 28.36, 43.19, 55.79, 55.87, 78.72, 108.31, 111.92, 114.25, 120.07, 121.36, 122.64, 125.78, 127.63, 128.26, 128.84, 129.50, 129.28, 131.76, 139.13, 144.52, 145.12, 147.27, 148.92, 149.85, 152.90. – MS: m/z (%) = 517 (100) $[M]^+$, 516 (80). – Anal. for $C_{30}H_{27}N_7O_2$: calcd. C 69.62, H 5.26, N 18.94; found C 69.41, H 5.51, N 18.71.

*8,9-Dimethoxy-3-(7-methyl-2-(4-methylphenyl)-2H-pyrazolo[3,4-d]pyridazin-4-yl)-1-phenyl-1,5,6,10b-tetrahydro-[1,2,4]triazolo[3,4-a]isoquinoline (**10b**)*

Red crystals, m. p. 220 °C, 87 % yield. – IR (KBr): no C=O bands. – ^{1}H NMR (DMSO): δ = 2.49 (s, 3H), 2.58 (s, 3H), 2.72 (m, 1H), 3.19 (m, 1H), 3.71 (s, 3H), 3.88 (m, 1H), 3.95 (s, 3H), 4.18 (m, 1H), 6.70 (s, 1H), 6.78 (s, 1H), 6.82 (s, 1H), 7.02 – 8.07 (m, 9H), 9.27 (s, 1H). – ^{13}C NMR (DMSO): δ = 19.01, 21.10, 28.34, 43.21, 55.73, 55.95, 78.76, 108.69, 111.42, 114.63, 119.86, 121.31, 121.70, 125.58, 127.34, 128.51, 129.27, 130.03, 131.19, 136.58, 137.99, 139.73, 144.18, 147.43, 148.97, 149.21, 153.92. – MS: m/z (%) = 531 (69) $[M]^+$, 530 (100), 91 (97), 77 (81). – Anal. for $C_{31}H_{29}N_7O_2$: calcd. C 70.04, H 5.50, N 18.44; found C 70.31, H 5.32, N 18.11.

*8,9-Dimethoxy-3-(7-methyl-2-(4-chlorophenyl)-2H-pyrazolo[3,4-d]pyridazin-4-yl)-1-phenyl-1,5,6,10b-tetrahydro-[1,2,4]triazolo[3,4-a]isoquinoline (**10c**)*

Red crystals, m. p. 238 °C, 89 % yield. – IR (KBr): no C=O bands. – ^{1}H NMR (DMSO): δ = 2.50 (s, 3H), 2.75 (m, 1H), 3.04 (m, 1H), 3.53 (s, 3H), 3.72 (s, 3H), 3.92 (m, 1H), 4.55 (m, 1H), 6.77 (s, 1H), 6.79 (s, 1H), 6.81 (s, 1H), 7.31 – 8.24 (m, 9H), 9.33 (s, 1H). – MS: m/z (%) = 553 (26) $[M+2]^+$, 552 (51) $[M+2–H]^+$, 551 (65) $[M]^+$, 550 (95) $[M–H]^+$, 77 (100). – Anal. for $C_{30}H_{26}ClN_7O_2$: calcd. C 65.27, H 4.75, Cl 6.42, N 17.76; found C 65.11, H 4.62, Cl 6.40, N 17.71.

*8,9-Dimethoxy-3-(7-methyl-2-phenyl-2H-pyrazolo[3,4-d]-pyridazin-4-yl)-1-(4-methylphenyl)-1,5,6, 10b-tetrahydro-[1,2,4]triazolo[3,4-a]isoquinoline (**10d**)*

Red crystals, m. p. 232 °C, 88 % yield. – IR (KBr): no C=O bands. – ^{1}H NMR (DMSO): δ = 2.26 (s, 3H), 2.51 (s,

3H), 2.73 (m, 1H), 3.04 (m, 1H), 3.53 (s, 3H), 3.71 (s, 3H), 3.90 (m, 1H), 4.50 (m, 1H), 6.38 (s, 1H), 6.75 (s, 1H), 6.79 (s, 1H), 7.13 – 8.22 (m, 9H), 9.31 (s, 1H). – ^{13}C NMR (DMSO): δ = 18.78, 20.67, 28.23, 42.93, 55.74, 56.12, 78.63, 108.91, 111.72, 114.95, 120.41, 122.36, 125.86, 127.79, 127.98, 128.24, 129.47, 129.63, 130.84, 131.07, 139.06, 141.96, 144.46, 147.85, 148.44, 149.83, 153.91. – MS: m/z (%) = 531 (62) $[M]^+$, 367 (100). – Anal. for $C_{31}H_{29}N_7O_2$: calcd. C 70.04, H 5.50, N 18.44; found C 70.10, H 5.32, N 18.33.

*8,9-Dimethoxy-3-(7-methyl-2-(4-methylphenyl)-2H-pyrazolo[3,4-d]pyridazin-4-yl)-1-(4-methylphenyl)-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]isoquinoline (**10e**)*

Red crystals, m. p. 228 °C, 88 % yield. – IR (KBr): no C=O bands. – ^{1}H NMR (DMSO): δ = 2.29 (s, 3H), 2.38 (s, 3H), 2.57 (s, 3H), 2.78 (m, 1H), 3.26 (m, 1H), 3.69 (s, 3H), 3.88 (m, 1H), 3.96 (s, 3H), 4.21 (m, 1H), 6.67 (s, 1H), 6.70 (s, 1H), 6.73 (s, 1H), 7.02 – 8.12 (m, 8H), 9.26 (s, 1H). – ^{13}C NMR (DMSO): δ = 18.29, 20.49, 21.73, 28.54, 42.97, 56.14, 56.56, 78.89, 108.76, 111.57, 115.68, 120.65, 122.73, 125.78, 127.54, 128.15, 129.44, 130.96, 131.23, 132.90, 136.75, 137.76, 142.92, 145.68, 147.25, 148.94, 149.50, 153.67. – MS: m/z (%) = 545 (66) $[M]^+$, 544 (100). – Anal. for $C_{32}H_{31}N_7O_2$: calcd. C 70.44, H 5.73, N 17.97; found C 70.31, H 5.92, N 18.20.

*8,9-Dimethoxy-3-(7-methyl-2-(4-chlorophenyl)-2H-pyrazolo[3,4-d]pyridazin-4-yl)-1-(4-methylphenyl)-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]isoquinoline (**10f**)*

Red crystals, m. p. 239 °C, 87 % yield. – IR (KBr): no C=O bands. – ^{1}H NMR (DMSO): δ = 2.30 (s, 3H), 2.54 (s, 3H), 2.83 (m, 1H), 3.19 (m, 1H), 3.72 (s, 3H), 3.87 (m, 1H), 3.91 (s, 3H), 4.25 (m, 1H), 6.37 (s, 1H), 6.58 (s, 1H), 6.62 (s, 1H), 7.02 – 8.29 (m, 8H), 9.26 (s, 1H). – MS: m/z (%) = 567 (16) $[M+2]^+$, 566 (38) $[M+2–H]^+$, 565 (53) $[M]^+$, 564 (100) $[M–H]^+$. – Anal. for $C_{31}H_{28}ClN_7O_2$: calcd. C 65.78, H 4.99, Cl 6.26, N 17.32; found C 65.51, H 5.21, Cl 6.11, N 17.63.

*8,9-Dimethoxy-3-(7-methyl-2-phenyl-2H-pyrazolo[3,4-d]-pyridazin-4-yl)-1-(4-chlorophenyl)-1,5,6,10b-tetrahydro-[1,2,4]triazolo[3,4-a]isoquinoline (**10g**)*

Red crystals, m. p. 237 °C, 86 % yield. – IR (KBr): no C=O bands. – ^{1}H NMR ($CDCl_3$): δ = 2.85 (m, 1H), 2.95 (m, 1H), 3.02 (s, 3H), 3.74 (s, 3H), 3.86 (s, 3H), 4.20 (m, 1H), 4.50 (m, 1H), 6.47 (s, 1H), 6.69 (s, 1H), 6.79 (s, 1H), 7.16 – 7.97 (m, 9H), 9.01 (s, 1H). – ^{13}C NMR ($CDCl_3$): δ = 18.52, 28.04, 43.45, 55.61, 56.03, 78.38, 108.15, 111.22, 114.43, 121.76, 122.01, 125.81, 125.98, 128.19, 128.71, 129.14, 129.44, 129.80, 130.53, 139.65, 144.07, 145.45, 147.95, 148.91, 149.99, 153.86. – MS: m/z (%) = 553 (5) $[M+2]^+$, 552 (12) $[M+2–H]^+$, 551 (17) $[M]^+$, 550 (55) $[M–H]^+$, 279 (100). – Anal. for $C_{30}H_{26}ClN_7O_2$: calcd. C 65.27, H 4.75, Cl 6.42, N 17.76; found C 65.01, H 4.32, Cl 6.11, N 17.42.

*8,9-Dimethoxy-3-(7-methyl-2-(4-methylphenyl)-2H-pyrazolo[3,4-d]pyridazin-4-yl)-1-(4-chlorophenyl)-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]isoquinoline (**10h**)*

Red crystals, m. p. 232 °C, 89 % yield. –

IR (KBr): no C=O bands. – ^{1}H NMR (DMSO): δ = 2.49 (s, 3H), 2.52 (s, 3H), 2.79 (m, 1H), 3.13 (m, 1H), 3.56 (s, 3H), 3.71 (s, 3H), 3.91 (m, 1H), 4.12 (m, 1H), 6.72 (s, 1H), 6.78 (s, 1H), 6.81 (s, 1H), 7.33 – 8.09 (m, 8H), 9.30 (s, 1H). – ^{13}C NMR (DMSO): δ = 19.03, 20.83, 28.12, 42.34, 55.98, 56.00, 78.76, 108.58, 112.43, 115.81, 119.44, 122.03, 125.34, 127.11, 128.35, 128.61, 129.26, 130.99, 131.33, 136.51, 138.42, 143.57, 145.04, 147.45, 148.98, 150.07, 152.98. – MS: m/z (%) = 567 (39) $[M+2]^+$, 566 (58) $[M+2–H]^+$, 565 (86) $[M]^+$, 564 (100) $[M–H]^+$. – Anal. for $C_{31}H_{28}ClN_7O_2$: calcd. C 65.78, H 4.99, Cl 6.26, N 17.32; found C 65.39, H 4.81, Cl 6.20, N 17.31.

*8,9-Dimethoxy-3-(7-methyl-2-(4-chlorophenyl)-2H-pyrazolo[3,4-d]pyridazin-4-yl)-1-(4-chlorophenyl)-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]isoquinoline (**10i**)*

Red crystals, m. p. 244 °C, 86 % yield. – IR (KBr): no C=O bands. – ^{1}H NMR (DMSO): δ = 2.53 (s, 3H), 2.86 (m, 1H), 3.29 (m, 1H), 3.76 (s, 3H), 3.98 (m, 1H), 4.12 (s, 3H), 4.26 (m, 1H), 6.72 (s, 1H), 6.78 (s, 1H), 6.82 (s, 1H), 7.34 – 8.29 (m, 8H), 9.28 (s, 1H). – MS: m/z (%) = 589 (25) $[M+4]^+$, 588 (37) $[M+4–H]^+$, 587 (27) $[M+2]^+$, 586 (67) $[M+2–H]^+$, 585 (67) $[M]^+$, 584 (100) $[M–H]^+$. – Anal. for $C_{30}H_{25}Cl_2N_7O_2$: calcd. C 61.44, H 4.30, Cl 12.09, N 16.72; found C 61.62, H 4.41, Cl 12.30, N 16.52.

*Synthesis of ethyl 4-(8,9-dimethoxy-1-aryl-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]isoquinoline-3-carbonyl)-1-aryl-1H-pyrazole-3-carboxylates (**13a – e**)*

These compounds were prepared as described above for the synthesis of **8** using hydrazonoyl halides **11** (1 mmol) in place of **1**. The products were crystallized from ethanol. The compounds prepared and their physical data are listed below.

*Ethyl 4-(8,9-dimethoxy-1-phenyl-1,5,6,10b-tetrahydro-[1,2,4]triazolo[3,4-a]isoquinoline-3-carbonyl)-1-phenyl-1H-pyrazole-3-carboxylate (**13a**)*

Orange crystals, m. p. 128 °C, 73 % yield. – IR (KBr): ν = 1739 (C=O), 1639 (C=O) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.19 (t, 3H), 2.74 (m, 1H), 3.00 (m, 1H), 3.59 (s, 3H), 3.86 (s, 3H), 3.88 (m, 1H), 4.11 (m, 1H), 4.30 (q, 2H), 6.65 (s, 1H), 6.69 (s, 1H), 6.72 (s, 1H), 6.95 – 7.77 (m, 10H), 8.54 (s, 1H). – ^{13}C NMR ($CDCl_3$): δ = 13.88, 27.89, 41.95,

55.81, 55.95, 61.65, 78.00, 108.36, 111.25, 114.34, 120.13, 121.06, 122.71, 127.86, 128.06, 129.03, 129.22, 129.52, 131.24, 138.87, 144.05, 145.92, 147.65, 148.81, 149.22, 162.54, 176.33. – MS: m/z (%) = 551 (56) $[M]^+$, 550 (100), 77 (88). – Anal. for $C_{31}H_{29}N_5O_5$: calcd. C 67.50, H 5.30, N 12.70; found C 67.41, H 5.50, N 12.51.

*Ethyl 4-(8,9-dimethoxy-1-phenyl-1,5,6,10b-tetrahydro-[1,2,4]triazolo[3,4-a]isoquinoline-3-carbonyl)-1-(4-methylphenyl)-1H-pyrazole-3-carboxylate (**13b**)*

Orange crystals, m. p. 134 °C, 74 % yield. – IR (KBr): ν = 1671 (C=O), 1634 (C=O) cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.15 (t, 3H), 2.34 (s, 3H), 2.70 (m, 1H), 3.00 (m, 1H), 3.55 (s, 3H), 3.82 (s, 3H), 3.85 (m, 1H), 4.08 (q, 2H), 4.30 (m, 1H), 6.61 (s, 1H), 6.65 (s, 1H), 6.69 (s, 1H), 6.91 – 7.60 (m, 9H), 8.46 (s, 1H). – ^{13}C NMR ($CDCl_3$): δ = 13.88, 20.95, 27.85, 41.91, 55.79, 55.95, 61.60, 77.92, 108.39, 111.30, 114.33, 119.95, 121.02, 122.54, 127.87, 128.14, 129.04, 129.22, 130.03, 131.12, 138.09, 144.00, 145.68, 147.61, 148.79, 149.22, 162.53, 176.36. – MS: m/z (%) = 565 (58) $[M]^+$, 564 (100). – Anal. for $C_{32}H_{31}N_5O_5$: calcd. C 67.95, H 5.52, N 12.38; found C 67.84, H 5.76, N 12.67.

*Ethyl 4-(8,9-dimethoxy-1-phenyl-1,5,6,10b-tetrahydro-[1,2,4]triazolo[3,4-a]isoquinoline-3-carbonyl)-1-(4-chlorophenyl)-1H-pyrazole-3-carboxylate (**13c**)*

Orange crystals, m. p. 150 °C, 73 % yield. – IR (KBr): ν = 1743 (C=O), 1637 (C=O) cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.19 (t, 3H), 2.74 (m, 1H), 3.00 (m, 1H), 3.59 (s, 3H), 3.87 (s, 3H), 3.90 (m, 1H), 4.10 (q, 2H), 4.30 (m, 1H), 6.67 (s, 1H), 6.69 (s, 1H), 6.72 (s, 1H), 6.96 – 7.72 (m, 9H), 8.51 (s, 1H). – ^{13}C NMR ($CDCl_3$): δ = 13.87, 27.89, 41.96, 55.82, 55.97, 61.76, 78.08, 108.36, 111.26, 114.40, 121.19, 121.25, 122.98, 125.72, 127.79, 128.10, 129.26, 129.70, 131.09, 137.39, 143.98, 146.13, 147.68, 148.85, 149.18, 162.30, 176.16. – MS: m/z (%) = 587 (29) $[M+2]^+$, 586 (46) $[M+2–H]^+$, 585 (63) $[M]^+$, 584 (100) $[M–H]^+$. – Anal. for $C_{31}H_{28}ClN_5O_5$: calcd. C 63.53, H 4.82, N 11.95, Cl 6.05; found C 63.73, H 5.09, N 12.22, Cl 5.91.

*Ethyl 4-(8,9-dimethoxy-1-(4-methylphenyl)-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]isoquinoline-3-carbonyl)-1-phenyl-1H-pyrazole-3-carboxylate (**13d**)*

Orange crystals, m. p. 118 °C, 75 % yield. – IR (KBr): ν = 1743 (C=O), 1635 (C=O) cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.20 (t, 3H), 2.30 (s, 3H), 2.76 (m, 1H), 2.96 (m, 1H), 3.60 (s, 3H), 3.86 (s, 3H), 4.00 (m, 1H), 4.12 (q, 2H), 4.34 (m, 1H), 6.63 (s, 1H), 6.68 (s, 1H), 6.71 (s, 1H), 7.11 – 7.76 (m, 9H), 8.53 (s, 1H). – ^{13}C NMR ($CDCl_3$): δ = 13.90, 20.58, 27.92, 41.99, 55.83, 55.95, 61.64, 78.46, 108.56, 111.25, 114.78, 120.14, 122.80, 125.76, 127.80, 128.03, 128.24, 129.52, 129.73, 130.78, 131.21, 138.91, 141.79, 147.60, 148.78, 149.03, 173.67, 176.21. – MS: m/z (%) = 565 (44) $[M]^+$, 564 (100), 563 (99). – Anal. for $C_{32}H_{31}N_5O_5$: calcd. C 67.95, H 5.52, N 12.38; found C 67.61, H 5.32, N 12.61.

*Ethyl 4-(8,9-dimethoxy-1-(4-chlorophenyl)-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]isoquinoline-3-carbonyl)-1-phenyl-1H-pyrazole-3-carboxylate (**13e**)*

Orange crystals, m. p. 118 °C, 72 % yield. – IR (KBr): ν = 1743 (C=O), 1643 (C=O) cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.16 (t, 3H), 2.74 (m, 1H), 3.00 (m, 1H), 3.62 (s, 3H), 3.85 (s, 3H), 3.90 (m, 1H), 4.15 (m, 1H), 4.30 (q, 2H), 6.27 (s, 1H), 6.55 (s, 1H), 6.60 (s, 1H), 6.64 – 7.75 (m, 9H), 8.50 (s, 1H). – ^{13}C NMR ($CDCl_3$): δ = 13.87, 27.93, 41.95, 55.92, 55.99, 61.69, 77.87, 108.10, 111.34, 114.41, 120.11, 122.63, 124.39, 127.87, 128.06, 128.91, 129.15, 129.56, 131.21, 138.80, 145.09, 145.93, 147.76, 148.95, 149.54, 162.40, 176.41. – MS: m/z (%) = 587 (30) $[M+2]^+$, 586 (57) $[M+2–H]^+$, 585 (100) $[M]^+$. – Anal. for $C_{31}H_{28}ClN_5O_5$: calcd. C 63.53, H 4.82, Cl 6.05, N 11.95; found C 63.82, H 4.66, Cl 6.30, N 11.80.

*Synthesis of 4-(8,9-dimethoxy-1-aryl-1,5,6,10b-tetrahydro-[1,2,4]triazolo[3,4-a]isoquinolin-3-yl)-2-aryl-2,6-dihydropyrazolo[3,4-d]pyridazin-7-ones (**14a – e**)*

These compounds were prepared as described above for the synthesis of **10** using the 3-ethoxy-4-carbonylpyrazole derivatives **13** instead of the 3-acetyl-4-carbonylpyrazole derivatives **8**. The products were crystallized from dimethyl formamide. The compounds prepared and their physical data are listed below.

*4-(8,9-Dimethoxy-1-phenyl-1,5,6,10b-tetrahydro[1,2,4]-triazolo[3,4-a]isoquinolin-3-yl)-2-phenyl-2,6-dihydropyrazolo[3,4-d]pyridazin-7-one (**14a**)*

Orange crystals, m. p. 260 °C, 83 % yield. – IR (KBr): ν = 3159 (NH), 1693 (C=O) cm^{-1}. – ^1H NMR (DMSO): δ = 2.77 (m, 1H), 2.85 (m, 1H), 3.72 (s, 3H), 3.78 (s, 3H), 3.83 (m, 1H), 4.24 (m, 1H), 6.66 (s, 1H), 6.74 (s, 1H), 6.79 (s, 1H), 6.86 – 8.10 (m, 10H), 9.13 (s, 1H), 12.71 (s, 1H). – ^{13}C NMR (DMSO): δ = 26.70, 42.29, 55.44, 55.54, 76.90, 109.10, 111.81, 113.40, 117.44, 119.36, 120.46, 120.97, 126.61, 128.17, 128.35, 128.75, 129.62, 132.35, 138.90, 142.20, 145.95, 147.23, 147.84, 148.51, 155.77. – MS: m/z (%) = 519 (46) $[M]^+$, 518 (85), 91 (100). – Anal. for $C_{29}H_{25}N_7O_3$: calcd. C 67.04, H 4.85, N 18.87; found C 67.30, H 4.61, N 18.50.

*4-(8,9-Dimethoxy-1-phenyl-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]isoquinolin-3-yl)-2-(4-methylphenyl)-2,6-dihydropyrazolo[3,4-d]pyridazin-7-one (**14b**)*

Orange crystals, m. p. 230 °C, 84 % yield. – IR (KBr): ν = 3200 (NH), 1681 (C=O) cm^{-1}. – ^1H NMR (DMSO): δ =

2.37 (s, 3H), 2.73 (m, 1H), 2.84 (m, 1H), 3.52 (s, 3H), 3.71 (s, 3H), 3.79 (m, 1H), 4.21 (m, 1H), 6.63 (s, 1H), 6.72 (s, 1H), 6.77 (s, 1H), 6.86 – 7.95 (m, 9H), 9.05 (s, 1H), 12.79 (s, 1H). – ^{13}C NMR (DMSO): δ = 20.52, 26.73, 42.33, 55.43, 55.55, 76.93, 108.96, 111.74, 113.40, 117.42, 119.41, 120.54, 120.57, 126.45, 128.17, 128.38, 129.08, 130.08, 132.37, 138.57, 142.26, 145.97, 146.03, 147.22, 148.48, 155.85. – MS: m/z (%) = 533 (37) $[M]^+$, 532 (87), 91 (100). – Anal. for $C_{30}H_{27}N_7O_3$: calcd. C 67.53, H 5.10, N 18.38; found C 67.61, H 4.90, N 18.71.

*4-(8,9-Dimethoxy-1-phenyl-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]isoquinolin-3-yl)-2-(4-chlorophenyl)-2,6-dihydropyrazolo[3,4-d]pyridazin-7-one (**14c**)*

Brown crystals, m. p. 243 °C, 85 % yield. – IR (KBr): ν = 3166 (NH), 1685 (C=O) cm^{-1}. – ^{1}H NMR (DMSO): δ = 2.76 (m, 1H), 2.85 (m, 1H), 3.54 (s, 3H), 3.78 (s, 3H), 3.81 (m, 1H), 4.29 (m, 1H), 6.62 (s, 1H), 6.75 (s, 1H), 6.78 (s, 1H), 6.82 – 8.11 (m, 9H), 9.11 (s, 1H), 12.71 (s, 1H). – ^{13}C NMR (DMSO): δ = 26.71, 42.32, 55.47, 55.54, 76.93, 109.20, 111.92, 113.78, 117.46, 119.46, 120.42, 120.89, 126.63, 128.27, 128.60, 128.81, 129.63, 132.38, 138.92, 142.34, 146.02, 146.98, 147.81, 148.59, 155.74. – MS: m/z (%) = 555 (20) $[M+2]^+$, 554 (24) $[M+2–H]^+$, 553 (66) $[M]^+$, 552 (53) $[M–H]^+$, 91 (100). – Anal. for $C_{29}H_{24}ClN_7O_3$: calcd. C 62.87, H 4.37, Cl 6.40, N 17.70; found C 62.71, H 4.22, Cl 6.33, N 17.92.

*4-(8,9-Dimethoxy-1-(4-methylphenyl)-1,5,6,10b-tetrahydro-[1,2,4]triazolo[3,4-a]isoquinolin-3-yl)-2-phenyl-2,6-dihydropyrazolo[3,4-d]pyridazin-7-one (**14d**)*

Orange crystals, m. p. 230 °C, 85 % yield. – IR (KBr): ν = 3352 (NH), 1712 (C=O) cm^{-1}. – ^{1}H NMR (DMSO): δ = 2.33 (s, 3H), 2.81 (m, 1H), 2.96 (m, 1H), 3.72 (s, 3H), 3.90 (s, 3H), 3.98 (m, 1H), 4.19 (m, 1H), 6.69 (s, 1H), 6.71 (s, 1H), 6.81 (s, 1H), 6.85 – 7.95 (m, 9H), 8.96 (s, 1H), 12.76 (s, 1H). – ^{13}C NMR (DMSO): δ = 20.52, 26.74, 42.37, 55.43, 55.56, 76.95, 109.00, 111.79, 113.42, 117.39, 119.45, 120.50, 120.59, 126.46, 128.27, 128.39, 129.09, 130.12, 132.33, 138.61, 142.29, 145.99, 146.05, 147.18, 148.41, 155.83. – MS: m/z (%) = 533 (18) $[M]^+$, 532 (35), 77 (100). – Anal. for $C_{30}H_{27}N_7O_3$: calcd. C 67.53, H 5.10, N 18.38; found C 67.41, H 4.90, N 18.31.

*4-(8,9-Dimethoxy-1-(4-chlorophenyl)-1,5,6,10b-tetrahydro-[1,2,4]triazolo[3,4-a]isoquinolin-3-yl)-2-phenyl-2,6-dihydropyrazolo[3,4-d]pyridazin-7-one (**14e**)*

Orange crystals, m. p. 234 °C, 84 % yield. – IR (KBr): ν = 3228 (NH), 1685 (C=O) cm^{-1}. – ^{1}H NMR (DMSO): δ = 2.74 (m, 1H), 2.85 (m, 1H), 3.56 (s, 3H), 3.72 (s, 3H), 3.81 (m, 1H), 4.19 (m, 1H), 6.63 (s, 1H), 6.68 (s, 1H), 6.79 (s, 1H), 7.32 – 8.09 (m, 9H), 9.12 (s, 1H), 12.74 (s, 1H). – ^{13}C NMR (DMSO): δ = 26.77, 42.40, 55.52, 55.60, 76.80, 108.74, 111.82, 114.74, 117.48, 120.63, 120.67, 120.71, 126.76, 128.14, 128.18, 128.86, 129.74, 132.25, 138.95, 142.25, 144.90, 147.32, 148.39, 148.59, 155.90. – MS: m/z (%) = 555 (22) $[M+2]^+$, 554 (59) $[M+2–H]^+$, 553 (55) $[M]^+$, 552 (98) $[M–H]^+$, 125 (100). – Anal. for $C_{29}H_{24}ClN_7O_3$: calcd. C 62.87, H 4.37, Cl 6.40, N 17.70; found C 62.53, H 4.51, Cl 6.61, N 17.71.

*Synthesis of [4-(8,9-dimethoxy-1-aryl-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]isoquinoline-3-carbonyl)-isoxazol-3-yl]arylmethanones (**16a**–**f**)*

A mixture of equimolar amounts of the appropriate enaminone **5** and hydroximoyl chloride **15** (5 mmol each) was stirred for 3 h, during which the compounds dissolved, and the corresponding adduct **16** was precipitated. The solid was collected and crystallized from acetonitrile. The compounds prepared and their physical data are listed below.

*[4-(8,9-Dimethoxy-1-phenyl-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]isoquinoline-3-carbonyl)isoxazol-3-yl]phenylmethanone (**16a**)*

Orange crystals, m. p. 154 °C, 75 % yield. – IR (KBr): ν = 1693 (C=O), 1647 (C=O) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.69 (m, 1H), 2.83 (m, 1H), 3.57 (s, 3H), 3.75 (m, 1H), 3.86 (s, 3H), 3.99 (m, 1H), 6.63 (s, 1H), 6.65 (s, 1H), 6.71 (s, 1H), 6.99 – 7.94 (m, 10H), 9.39 (s, 1H). – ^{13}C NMR ($CDCl_3$): δ = 27.72, 41.89, 55.80, 55.98, 78.31, 108.28, 111.31, 114.78, 120.10, 121.68, 127.21, 128.01, 128.68, 129.32, 129.91, 134.34, 135.66, 143.43, 147.66, 148.08, 148.94, 159.57, 162.51, 173.45, 186.33. – MS: m/z (%) = 508 (11) $[M]^+$, 104 (100). – Anal. for $C_{29}H_{24}N_4O_5$: calcd. C 68.49, H 4.76, N 11.02; found C 68.41, H 4.82, N 11.21.

*[4-(8,9-Dimethoxy-1-(4-methylphenyl)-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]isoquinoline-3-carbonyl)-isoxazol-3-yl]phenylmethanone (**16b**)*

Orange crystals, m. p. 150 °C, 80 % yield. – IR (KBr): ν = 1689 (C=O), 1651 (C=O) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.33 (s, 3H), 2.64 (m, 1H), 2.81 (m, 1H), 3.64 (s, 3H), 3.68 (m, 1H), 3.86 (s, 3H), 4.02 (m, 1H), 6.62 (s, 1H), 6.63 (s, 1H), 6.70 (s, 1H), 7.04 – 7.94 (m, 9H), 9.37 (s, 1H). – ^{13}C NMR ($CDCl_3$): δ = 20.64, 27.80, 41.99, 56.98, 56.07, 78.19, 107.82, 111.10, 115.40, 120.62, 126.01, 127.56, 127.65, 128.23, 129.92, 129.99, 134.58, 135.20, 142.12, 147.14, 148.64, 149.68, 159.51, 162.54, 173.11, 187.01. – MS: m/z (%) = 522 (6) $[M]^+$, 104 (100). – Anal. for $C_{30}H_{26}N_4O_5$: calcd. C 68.95, H 5.02, N 10.72; found C 68.72, H 5.31, N 10.41.

*[4-(8,9-Dimethoxy-1-(4-chlorophenyl)-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]isoquinoline-3-carbonyl)-isoxazol-3-yl]phenylmethanone (**16c**)*

Yellow crystals, m. p. 162 °C, 77 % yield. – IR (KBr): ν = 1693 (C=O), 1651 (C=O) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.71 (m, 1H), 2.80 (m, 1H), 3.62 (s, 3H), 3.78 (m, 1H), 3.87 (s, 3H), 3.92 (m, 1H), 6.54 (s, 1H), 6.56 (s, 1H), 6.66 (s, 1H), 7.00 – 7.93 (m, 9H), 9.36 (s, 1H). – ^{13}C NMR ($CDCl_3$): δ = 27.78, 41.91, 55.92, 56.01, 78.13, 107.97, 111.37, 115.42, 120.07, 126.36, 127.07, 127.94, 128.69, 129.23, 129.90, 134.40, 135.59, 142.22, 147.78, 148.40, 149.08, 159.51, 162.50, 173.57, 186.17. – MS: m/z (%) = 544 (2) $[M+2]^+$, 543 (3) $[M+2–H]^+$, 542 (11) $[M]^+$, 541 (9) $[M–H]^+$, 105 (89), 51 (100). – Anal. for $C_{29}H_{23}ClN_4O_5$: calcd. C 64.15, H 4.27, Cl 6.53, N 10.32; found C 64.16, H 4.41, Cl 6.43, N 10.11.

*[4-(8,9-Dimethoxy-1-phenyl-1,5,6,10b-tetrahydro[1,2,4]-triazolo[3,4-a]isoquinoline-3-carbonyl)isoxazol-3-yl]-(2-thienyl)methanone (**16d**)*

Orange crystals, m. p. 164 °C, 78 % yield. – IR (KBr): ν = 1674 (C=O), 1647 (C=O), 1596 (C=C) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.72 (m, 1H), 2.89 (m, 1H), 3.56 (s, 3H), 3.78 (m, 1H), 3.86 (s, 3H), 4.04 (m, 1H), 6.64 (s, 1H), 6.66 (s, 1H), 6.70 (s, 1H), 6.95 – 7.81 (m, 8H), 9.30 (s, 1H). – ^{13}C NMR ($CDCl_3$): δ = 27.75, 41.94, 55.78, 55.95, 78.41, 108.30, 111.32, 114.78, 119.76, 121.59, 127.14, 128.08, 128.44, 129.25, 130.46, 136.51, 142.61, 143.36, 147.60, 148.21, 148.91, 159.14, 162.42, 173.50, 177.56. – MS: m/z (%) = 514 (9) $[M]^+$, 111 (100). – Anal. for $C_{27}H_{22}N_4O_5S$: calcd. C 63.03, H 4.31, N 10.89, S 6.22; found C 63.21, H 4.60, N 10.61, S 6.12.

*[4-(8,9-Dimethoxy-1-(4-methylphenyl)-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]isoquinoline-3-carbonyl)-isoxazol-3-yl](2-thienyl)methanone (**16e**)*

Orange crystals, m. p. 152 °C, 78 % yield. – IR (KBr): ν = 1674 (C=O), 1651 (C=O) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.31 (s, 3H), 2.71 (m, 1H), 2.95 (m, 1H), 3.52 (s, 3H), 3.72 (m, 1H), 3.86 (s, 3H), 4.07 (m, 1H), 6.61 (s, 1H), 6.64 (s, 1H), 6.68 (s, 1H), 7.00 – 7.80 (m, 7H), 9.28 (s, 1H). – ^{13}C NMR ($CDCl_3$): δ = 20.63, 27.75, 41.97, 55.78, 55.94, 78.90, 108.51, 111.32, 115.30, 119.81, 121.59, 127.00, 128.24, 128.43, 129.76, 131.45, 136.49, 141.02, 142.63, 147.52, 148.02, 148.86, 159.15, 162.35, 173.28, 177.56. – MS: m/z (%) = 528 (3) $[M]^+$, 111 (100). – Anal. for $C_{28}H_{24}N_4O_5S$: calcd. C 63.63, H 4.58, N 10.60, S 6.05; found C 63.42, H 4.56, N 10.34, S 5.83.

*[4-(8,9-Dimethoxy-1-(4-chlorophenyl)-1,5,6,10b-tetrahydro[1,2,4]triazolo[3,4-a]isoquinoline-3-carbonyl)-isoxazol-3-yl](2-thienyl)methanone (**16f**)*

Yellow crystals, m. p. 158 °C, 80 % yield. – IR (KBr): ν = 1674 (C=O), 1651 (C=O) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.72 (m, 1H), 2.90 (m, 1H), 3.62 (s, 3H), 3.80 (m, 1H), 3.87 (s, 3H), 3.97 (m, 1H), 6.57 (s, 1H), 6.68 (s, 1H), 6.70 (s, 1H), 6.88 – 7.83 (m, 7H), 9.27 (s, 1H). – ^{13}C NMR ($CDCl_3$): δ = 27.85, 42.01, 55.78, 55.93, 78.25, 108.01, 111.01, 115.42, 119.82, 121.58, 127.01, 128.03, 128.49, 129.18, 131.45, 136.59, 141.03, 142.63, 147.51, 148.03, 148.91, 159.16, 162.40, 173.29, 177.57. – MS: m/z (%) = 550 (6) $[M+2]^+$, 549 (10) $[M+2–H]^+$, 548 (15) $[M]^+$, 547 (7) $[M–H]^+$, 111 (100). – Anal. for $C_{27}H_{21}ClN_4O_5S$: calcd. C 59.08, H 3.86, Cl 6.46, N 10.21, S 5.83; found C 59.33, H 3.99, Cl 6.31, N 10.50, S 5.72.

Antibacterial activity

The antibacterial activities of the compounds were assayed according to Bauer [39]. 100 μL of the bacterial spore suspensions was spread onto plates containing Mueller-Hinton agar. The disc diffusion method for bacteria was used to study the sensitivity of the pathogenic bacterial species to the tested compounds. Plates inoculated with *Staphylococcus aureus* Gram (+), *Bacillus subtilis* Gram (+), *Escherichia coli* Gram (–) and *Neisseria gonorrhoeae* Gram (–) were incubated at 35 ± 2 °C for 24 h; the diameter of the inhibition zones was then measured. Standard discs of tetracycline and DMSO discs were used as positive and negative controls, respectively [40].

The minimum inhibitory concentration (MIC) of the most potent antibacterial compounds was determined by the broth microdilution method by a whole-cell assay in 96-well microtitre format [41]. Bacterial cell suspensions with an initial cell optical density at 600 nm (OD600) of 0.001 in nutrient broth (DIFCO) medium were inoculated with serial bi-fold dilutions (0 – 280 $\mu g\,mL^{-1}$) of the tested compound. The growth was measured by OD600 after 48 h. The MIC is defined as the least concentration of the antibacterial compound that completely inhibits the growth of a particular bacterial species under standardized *in vitro* conditions.

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