Full Paper

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Synthesis and prediction of toxicological and pharmacological properties of Schiff bases containing arylfuran and pyrazole moiety

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Abstract: A series of new azomethines with pyrazole and arylfuran fragments – 4-[{(5-Arylfuran-2-yl)methylene}amino]-1,2-dihydro-1,5-dimethyl-2-phenyl-3H-pyrazol-3-one – are synthesized by the condensation of 4-aminoantipyrine and 5-arylfurfural using a Monowave 50 synthesis reactor. The structures of the obtained compounds are confirmed with 1H NMR and IR spectroscopy.

Keywords: 4-Aminoantipyrine, Aryl furan derivatives, Schiff bases, Probable pharmacological activity, Predicted toxicity

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Introduction

In the pharmaceutical and chemical industries, 4-aminoantipyrine is used as a key intermediate for the synthesis of biologically active compounds and potential drugs [1]. Antipyrine derivatives exhibit analgesic, anti-inflammatory, antimicrobial, and antitumor activities [2]. Among 4-aminoantipyrine derivatives, Schiff bases are important, as they possess a significant number of biomedical properties [3–5]. For example, the authors of [6] found that substances derived from 4-aminoantipyrine and substituted benzaldehydes can serve as potential antibacterial drugs. The presence of methoxy or hydroxy groups in the benzene ring in different positions significantly increases the antimicrobial and antibacterial properties [7].

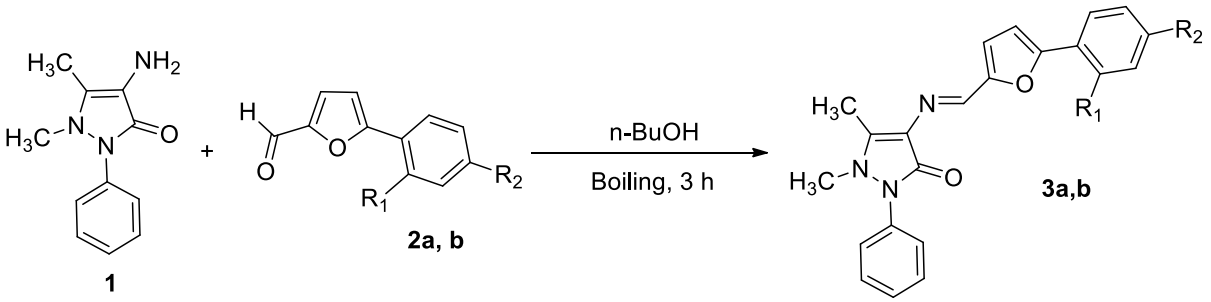
In addition to the above properties, azomethines derived from 4-aminoantipyrine exhibit antioxidant effects which are even better than those of a number of known antioxidants, such as butyl hydroxyanisole. They also have low cytotoxicity and are promising drugs in the treatment of Alzheimer's disease [8]. Antibacterial, antifungal, antitumor, and antileukemia activities are exhibited by transition metal complexes with the specified Schiff bases [9]. For example, complexes of Copper, Nickel, and Vanadium with 4-aminoantipyrine azomethines have better antibacterial properties than the well-known antibiotic streptomycin [10].

Among arylfurans, substances with various biological activities it has also been found that can be potential medicines [11]. For example, the well-known Dantrolene, Clodanolen, and Azimilide contain arylfuran fragments in their structure and have antiarrhythmic effects, being muscle antirelaxants [12]. Schiff compounds derived from 5-arylfuran-2-carbaldehydes, namely 3-substituted-4-[5-(2,4-dichlorophenyl)-2-furfurylidine]-amino-5-mercapto-1,2,4-triazoles, have shown antibacterial properties [13], and the study of azomethine based on isoniazid and 5-(2-nitrophenyl)-furfural demonstrated the prospect of its use in anticancer therapy [14], which, in turn, reveals the relevance of the study of Schiff bases based on 5-aryl furfural.

This work is devoted to the synthesis of compounds that combine the following biogenic fragments in one structure: arylfuran and pyrazole. The aim of this work is developing the conditions for the synthesis of Schiff bases containing arylfuran and pyrazole moiety, studying their spectral characteristics, and performing computer screening of biological properties and acute toxicity.

Results and discussion

According to the literature, the synthesis of Schiff compounds based on 4-aminoantipyrine was carried out in methanol for 12–14 hours [15] or in ethanol for 5–6 hours [6]. Substituted benzaldehydes were mainly used for the synthesis of Schiff's bases. The authors of [16] investigated the reaction of 4-aminoantipyrine with furfural. We have studied the interaction of 4-aminoantipyrine with 5-aryl furfural, which were obtained according to the method [17, 18]. In search of optimal conditions for the synthesis of azomethines based on 4-aminoantipyrine **1**, we replaced low-boiling alcohols with butanol. It was found that boiling 4-aminoantipyrine **1** and 5-(4-bromophenyl)furfural **2a** or 5-(2,4-dichlorophenyl)furfural **2b** in butanol for 3 hours controlling the reaction by TLC (eluent chloroform, Rf = 0.38 and 0.30 for **3a, b** respectively) and the yields of the corresponding azomethines **3a, b** were 71 and 86% respectively (Scheme 1).

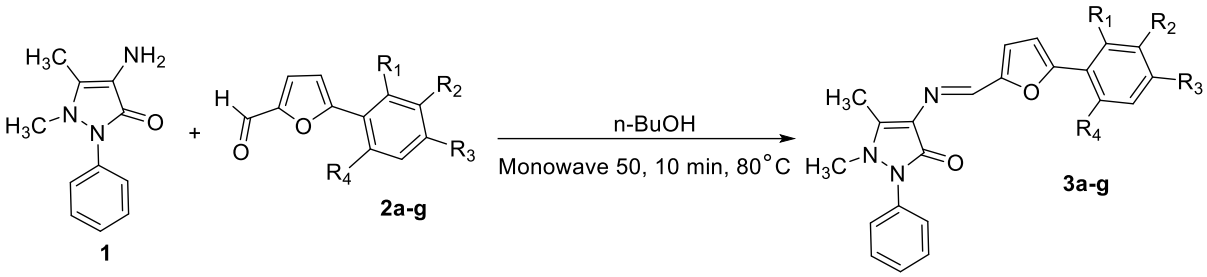


R^1 = H, R^2 = Br (**3a**); R^1 = R^2 = Cl (**3b**)

Scheme 1

Taking into account the long duration of this synthesis, the next step was to speed up the process of obtaining Schiff compounds. Therefore, we proposed a method for the preparation of azomethines with arylfuran and pyrazole fragments **3a–g** by condensation of 4-aminoantipyrine **1** with 5-arylfurfural **2a–g** in a Monowave 50 synthesis reactor [19]. In order to find out the optimal temperature and the reaction time we used azomethine **3a** as model substrate. The first attempt was to use the temperature of 120°C (close to boiling point of butanol) and time of 5 min but in this case the temperature of reaction mixture increased drastically up to 200°C therefore we chose the lower temperatures and noticed that the optimal temperature when no extra increase of temperature is observed was 80 °C. The next step was to determine the optimal reaction time; hence we conduct the synthesis for 5, 10, 15 and 20 minutes and observed that the yield of **3a** in the first case was 45 %, in second — 74 %, in third — 75%, and fourth — 70% (all yields were estimated on isolated compounds after filtration of crude products and recrystallization from butanol). Consequently, other azomethines **3b–g** were obtained in the reaction between 4-

aminoantipyrine **1** and corresponding 5-arylfurfural **2b-g** in butanol at 80°C for 10 minutes (Scheme 2). The yields of compounds in the Monovawe 50 reactor are in the range of 62-90%.



$R^1 = R^2 = R^4 = H$, $R^3 = Br$ (**3a**); $R^1 = R^2 = H$, $R^3 = R^4 = Cl$ (**3b**);
$R^1 = R^2 = H$, $R^3 = Cl$, $R^4 = NO_2$ (**3c**); $R^1 = R^2 = H$, $R^3 = NO_2$, $R^4 = OCH_3$ (**3d**);
$R^1 = R^2 = H$, $R^3 = NO_2$, $R^4 = Cl$ (**3e**); $R^1 = R^3 = H$, $R^2 = CF_3$, $R^4 = Cl$ (**3f**);
$R^1 = R^2 = R^4 = H$, $R^3 = C(O)CH_3$ (**3g**)

Scheme 2

The structures of the obtained compounds were proved by means of IR, 1H NMR spectroscopy and mass spectrometry. For the synthesized Schiff bases **3a**–**g**, a singlet with a chemical shift in the range of 9.36–9.50 ppm was observed in each ^{1}H NMR spectra, which corresponds to the azomethine group –CH=N. Two singlet signals with an inegral intensity of 3 with chemical shifts in the range of 3.18–3.30 ppm and 2.43–2.46 ppm were also observed, indicating the presence of -NCH_3 and –CH_3 groups of the pyrazole fragment, respectively. The multiplet signals with chemical shifts of 7.00–8.50 ppm correspond to the aromatic protons of the aryl and furan fragments. Additionally, for compounds **3d** and **3g**, singlet signals with an integrated intensity of 3 with chemical shifts of 4.08 and 2.59 ppm were observed, indicating the presence of methoxy- and acetyl groups in the synthesized azomethines, respectively.

In the mass spectra of each of the seven synthesized compounds, a peak of the protonated molecular ion $[M+H]^+$ is observed, which allows to confirm the molecular weight of the obtained azomethines. For the substances containing halogen atoms (**3a**–**c**, **3e**-**f**), distinct peaks were observed in the mass spectra corresponding to different halogen isotopes: for chloro derivatives, these are ^{35}Cl and ^{37}Cl, and for bromo derivatives, ^{79}Br and ^{81}Br.

In the IR spectra of each of the synthesized compounds **3a**–**g**, characteristic absorption bands are observed, namely: 3024–3094 cm^{-1}, corresponding to the C–H vibrations of the aromatic fragments, 2931–2949 cm^{-1} — CH_3 vibrations from the N–CH_3 and C–CH_3 fragments of the 4-aminoantipyrine, 1632-1672 cm^{-1} — vibrations of the carbonyl group of the pyrazole cycle, 1590–1654 cm^{-1} — vibrations of the azomethine group of C=N

group, 1564–1595 cm^{-1} — vibrations of the C=C bond. For compounds **3d** and **3e** containing a nitro group, there are characteristic vibrations at 1506 and 1550 cm^{-1} corresponding to asymmetric vibrations of the NO_2 group; 1350 and 1342 cm^{-1} corresponding to symmetric vibrations of the NO_2. For compound **3d**, a absorption band at 1250 cm^{-1} is also observed, indicating the presence of vibrations of the ether bond C–O associated with the aromatic core, and for compound **3g**, an additional absorption band at 1673 cm^{-1} corresponding to the vibrations of C=O of the acetyl group.

Today, prediction of biological properties of compounds using computer screening is becoming increasingly popular. For the synthesized compounds **3a–g**, we calculated the following parameters: the probability of detecting certain types of biological activity, druglikeness and probable LD_{50} values using Internet resources: PASS online, OSIRIS Property Explorer, Gusar (for rat) [20, http://www.organic-chemistry.org/prog/peo/].

Table 1. Probability (Ra) of some types of biological activity of Schiff bases **3a**–**g**

Compound	Antiin-flammatory	Insulysin inhibitor	Analgesic	Antipyretic
3a	0.862	0.840	0.804	0.790
3b	0.853	0.805	0.815	0.663
3c	0.827	0.729	0.708	0.567
3d	0.831	0.773	0.677	0.738
3e	0.812	0.719	0.723	0.659
3f	0.835	0.765	0.810	0.625
3g	0.886	0.909	0.791	0.886

The results of computer screening of the biological activity of Schiff compounds **3a**–**g** are presented in Table 1. For the studied compounds, the PASS program predicts anti-inflammatory, insulin-inhibitory, analgesic, and antipyretic activities. Based on these results, it can be concluded that all compounds in the subsequent experiment will exhibit these types of activities with a high probability. According to the results of PASS software modeling, the investigated compounds are likely to exhibit anti-inflammatory activity in the range of 81.2–88.6%, insulin-inhibitory activity — 71.9–90.9%, analgesic activity — 67.7–81.5%, and antipyretic activity — 56.7–88.6%. Compound **3g**, which contains an acetyl group at the fourth position of the aryl furan fragment, is of particular interest; it is likely to have a combined effect: anti-inflammatory, insulin-inhibitory, and antipyretic. The value of Ra

acquires the highest analgesic activity for compound **3b**, which contains chlorine atoms in the second and fourth positions of the benzene nucleus of the aryl furan substituent.

For compounds **3a–g**, the OSIRIS Property Explorer program was used to calculate the drug-like criteria. These characteristics are shown in Table 2. The results of the calculation of the criteria for druglikeness indicates that the synthesized substances will not deviate from the Lipinski rules [21], namely, they will be bioavailable. It is worth noting that according to the values of the Lipinski parameters, compounds **3a**, **3b**, and **3g** are the most promising, since the overall Drug Score criterion acquires the highest values, namely 0.27, 0.26, and 0.30, respectively.

Table 2. Values of the criteria for the drug-like properties of compounds **3a**–**g**

Com-pound	Log P	Molecular weight	Number of hydrogen bond acceptors	Number of hydrogen bond donors	Number of rotatable bonds	«Drug Score» (DS)
3a	3.82	436.31	5	0	4	0.27
3b	4.31	426.30	5	0	4	0.26
3c	2.56	436.85	8	0	5	0.10
3d	2.61	446.46	9	0	6	0.17
3e	3.29	450.88	8	0	5	0.17
3f	4.55	459.85	5	0	5	0.08
3g	2.97	399.45	6	0	5	0.30

To evaluate the prospects of azomethines **3a**–**g** as potential biomedical drugs, an important characteristic is the acute toxicity value. To calculate these values, we used the GUSAR program (for the rat), according to which the obtained Schiff bases with pyrazole and arylfuran substituents are low toxic (class 4) or non-toxic (class 5). The results of the acute toxicity prediction were obtained in the form of LD_{50} values at different routes of administration (Table 3). In the case of intraperitoneal administration, the LD_{50} values for the synthesized Schiff bases with pyrazole and arylfuran substituents are in the range of 681–1239 mg/kg, and the toxicity class is 5. When the compounds are administered intravenously, the LD_{50} is observed to be 120–198 mg/kg, and the toxicity class is 4. The LD_{50} values for the oral route of administration for the studied compounds were 867–2718 mg/kg (toxicity classes 4 and 5). In case of subcutaneous injection, the LD_{50} values were 910–2598 mg/kg, class 4 and 5.

Table 3. Results of computer prediction of acute toxicity of Schiff bases **3a**–**g**

Compound	Intra-abdominal route of administration (IR)		Intravenous route of administration (IV)		Oral route of administration (Oral)		Subcutaneous route of administration (SC)	
	LD_{50} мг/кг	Class of toxicity	LD_{50} мг/кг	Class of toxicity	LD_{50} мг/кг	Class of toxicity	LD_{50} мг/кг	Class of toxicity
3a	1239	5	198	4	2012	5	1075	5
3b	857	5	167	4	2662	5	2598	5
3c	831	5	127	4	1377	4	1048	5
3d	681	5	120	4	1271	4	910	4
3e	902	5	131	4	867	4	930	4
3f	759	5	195	4	1095	4	943	4
3g	946	5	166	4	2718	5	1248	5

The results show an important argument for further experimental biological research.

Experimental

Instruments and methods

^{1}H NMR spectra were recorded on Varian Unity Plus 400 (400 MHz) spectrometer in DMSO-d_6 solutions using TMS as reference. Mass spectral analyses were performed using an Agilent 1100 series LC/MSD with API-ES/APCI mode (200 eV). The IR spectra were recorded on Shimadzu IRSpirit Spectrometer. Elemental analyses were accomplished using a Carlo Erba 1106 instrument. Melting points were determined using a Boetius device (Germany). Starting materials and solvents from the Merck company were used without additional purification.

Synthesis methods and characterization of compounds

General method of synthesis of Schiff bases 3a, b.

A mixture of 2.5 mmol of 4-aminoantipyrine **1**, 2.5 mmol of 5-(4-bromophenyl)furfural **2a** or 5-(2,4-dichlorophenyl)furfural **2b** in 25 ml of butanol was boiled (118°C) for 3 hours. After the reaction mixture cooled, the resulting precipitate was filtered off, washed with diethyl ether, dried and recrystallized from butanol. Compounds **3a** and **3b** were obtained with yields of 71% and 86% respectively.

Methodology for the synthesis of Schiff bases 3a–g in the Monowave 50 synthesis reactor.

4-Aminoantipyrine **1 (**0.42 mmol), 5-arylfurfural **2a**–**g** (0.42 mmol), and 4.2 ml of butanol were placed in a special G10 container (made of borosilicate glass) equipped with a

magnetic stirrer, and the tube was closed with a suitable silicone cap. The vial was placed in the synthesis reactor and the following step was selected in the settings: AFAP. The synthesis was carried out at 80°C for 10 minutes. The end of the reaction was monitored by TLC (chloroform). After the reaction mixture cooled, the resulting precipitate was filtered off, washed with diethyl ether, dried, and recrystallized from butanol. The yields of Schiff bases **3a**–**g** in the Monowave 50 reactor are 62–90%.

4-[{[5-(4-Bromophenyl)furan-2-yl]methylene}amino]-1,2-dihydro-1,5-dimethyl-2-phenyl-3H-pyrazol-3-one (**3a**).

Golden powder. Yield 74%, m.p. 190–191°C. FT-IR (ν, cm^{-1}): 3059 (C–H aromatic), 2948 (CH_3), 1637 (C=O), 1583 (HC=N), 1569 (C=C). ^{1}H NMR (DMSO-d_6), δ, ppm: 9.45 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.50–7.55 (m, 2H), 7.35–7.40 (m, 3H), 7.19 (d, *J* = 3.7 Hz, 1H), 7.07 (d, *J* = 3.6 Hz, 1H), 3.18 (s, 3H), 2.44 (s, 3H). MS (m/z): 436 (M^++1, ^{79}Br) and 438 (M^++1, ^{81}Br). Anal. calcd. for $C_{22}H_{18}BrN_3O_2$: C 60.56; H 4.16; N 9.63; found: C 60.31; H 4.31; N 9.49.

4-[{[5-(2,4-Dichlorophenyl)furan-2-yl]methylene}amino]-1,2-dihydro-1,5-dimethyl-2-phenyl-3H-pyrazol-3-one (**3b**).

Yellow powder. Yield 89%, m.p. 175–176°C. FT-IR (ν, cm^{-1}): 3074 (C–H aromatic), 2948 (CH_3), 1641 (C=O), 1604 (HC=N), 1595 (C=C). ^{1}H NMR (DMSO-d_6), δ, ppm: 9.47 (s, 1H), 7.93 (d, *J* = 8.8 Hz, 1H), 7.75 (s, 1H), 7.50–7.59 (m, 3H), 7.35–7.40 (m, 3H), 7.31 (d, *J* = 3.8 Hz, 1H), 7.12 (d, *J* = 3.8 Hz, 1H), 3.19 (s, 3H), 2.44 (s, 3H). MS (m/z): 426 (M^++1, ^{35}Cl) and 428 (M^++1, ^{35}Cl + ^{37}Cl). Anal. calcd. for $C_{22}H_{17}Cl_2N_3O_2$: C 61.98; H 4.02; N 9.86; found: C 60.76; H 4.16; N 9.63.

4-[{[5-(4-Chloro-2-nitrophenyl)furan-2-yl]methylene}amino]-1,2-dihydro-1,5-dimethyl-2-phenyl-3H-pyrazole-3-one (**3c**).

Orange powder. Yield 65%, m.p. 195–196°C. FT-IR (ν, cm^{-1}): 3091 (C–H aromatic), 2948 (CH_3), 1634 (C=O), 1597 (HC=N), 1571 (C=C), 1538 (NO_2 asymmetric), 1354 (NO_2 symmetric). ^{1}H NMR (DMSO-d_6), δ, ppm: 9.36 (s, 1H), 8.13 (d, *J* = 2.1 Hz, 1H), 7.95(d, *J* = 8.6 Hz, 1H), 7.83 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.32–7.40 (m, 3H), 7.12 (d, *J* = 3.8 Hz 1H), 7.09 (d, *J* = 3.8 Hz 1H), 3.19 (s, 3H), 2.43 (s,3H). MS (m/z): 437 (M^++1, ^{35}Cl). Anal. calcd. for $C_{22}H_{17}ClN_4O_4$: C 60.49; H 3.92; N 12.83; found: 60.37; H 3.77; N 12.65.

4-[{[5-(4-Nitro-2-methoxyphenyl)furan-2-yl]methylene}amino]-1,2-dihydro-1,5-dimethyl-2-phenyl-3H-pyrazol-3-one (**3d**).

Red powder. Yield 86%, m.p. 214–215°C. FT-IR (ν, cm^{-1}): 3026 (C–H aromatic), 2931 (CH_3), 1672 (C=O), 1654 (HC=N), 1590 (C=C), 1506 (NO_2 asymmetric), 1350 (NO_2 symmetric), 1250 (C–O aromatic). ^{1}H NMR (DMSO-d_6), δ, ppm: 9.48 (s, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.96 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.87 (d, *J* = 2.3 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.35–7.41 (m, 3H), 7.33 (d, *J* = 3.7 Hz, 1H), 7.13 (d, *J* = 3.7 Hz, 1H), 4.08 (s, 3H), 3.20 (s, 3H), 2.46 (s, 3H). MS (m/z): 433 (M^++1). Anal. calcd. for $C_{23}H_{20}N_4O_5$: C 63.88; H 4.66; N 12.96; found: C 63.71; H 4.53; N 12.79.

4-[{[5-(2-Chloro-4-nitrophenyl)furan-2-yl]methylene}amino]-1,2-dihydro-1,5-dimethyl-2-phenyl-3H-pyrazol-3-one (**3e**).

Brown-red powder. Yield 90%, m.p. 208–209°C. FT-IR (ν, cm^{-1}): 3094 (C–H aromatic), 2939 (CH_3), 1642 (C=O), 1590 (HC=N), 1564 (C=C), 1550 (NO_2 asymmetric), 1342 (NO_2 symmetric). ^{1}H NMR (DMSO-d_6), δ, ppm: 9.50 (s, 1H), 8.39 (br.s, 1H), 8.27–8.35 (m, 1H), 8.16–8.23 (m, 1H), 7.20–7.61 (m, 7H), 3.22 (s, 3H), 2.46 (t, 3H). MS (m/z): 437 (M^++1, ^{35}Cl). Anal. calcd. for $C_{22}H_{17}ClN_4O_4$: C 60.49; H 3.92; N 12.83; found: C 60.24; H 3.88; N 12.65.

4-[{[5-(2-Chloro-5-(trifluoromethyl)phenyl]furan-2-yl}methylene)-amino]-1,2-dihydro-1,5-dimethyl-2-phenyl-3H-pyrazole -3-one (**3f**).

Pale yellow powder. Yield 62%, m.p. 167–168°C. FT-IR (ν, cm^{-1}): 3039 (C-H aromatic), 2949 (CH_3), 1642 (C=O), 1610 (HC=N), 1564 (C=C). ^{1}H NMR (DMSO-d_6), δ, ppm: 9.50 (s, 1H), 8.17 (d, J = 2.3 Hz, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.73 (dd, J = 8.5, 2.4 Hz, 1H), 7.54 (t, J = 7.8 Hz, 2H), 7.44 (d, J = 3.7 Hz, 1H), 7.34–7.42 (m, 3H), 7.16 (d, J = 3.8 Hz, 1H), 3.20 (s, 3H), 2.44 (s, 3H). MS (m/z): 460 (M^++1). Anal. calcd. for $C_{23}H_{17}ClF_3N_3O_2$: C 60.07; H 3.73; N 9.14; found: C 60.21; H 3.55; N 9.03.

4-[{[5-(4-Acetyl)furan-2-yl]methylene}amino]-1,2-dihydro-1,5-dimethyl-2-phenyl-3H-pyrazol-3-one (**3g**).

Pale orange powder. Yield 84%, m.p. 213–214°C. FT-IR (ν, cm^{-1}): 3055 (C–H aromatic), 2936 (CH_3), 1673 (C=O acetic group), 1645 (C=O amide group) 1604 (HC=N), 1574 (C=C). ^{1}H NMR (DMSO-d_6), δ, ppm: 9.48 (s, 1H), 8.03 (d, *J* = 8.2 Hz, 2H), 7.92 (d, *J* = 8.2 Hz, 2H), 7.53 (t, *J* = 7.7 Hz, 2H), 7.36–7.41 (m, 3H), 7.34 (d, *J* = 3.5 Hz, 1H), 7.12 (d, *J* = 3.5 Hz,

1H), 3.19 (s, 3H), 2.59 (s, 3H), 2.46 (s, 3H). Anal. calcd. for $C_{24}H_{21}N_3O_3$: C 72.16;H 5.30; N 10.52; found: C 72.28; H 5.16; N 10.68.

Conclusions

Methods for the synthesis of Schiff bases containing arylfuran and pyrazole moiety have been developed. The analysis of the criteria for druglikeness properties of the obtained compounds indicates that they have no deviations from the Lipinski rules, i.e., they are bioavailable. According to the results of PASS software modeling, it was found that the obtained Schiff bases with arylfuran and pyrazole fragments with moderate and high probability in the experiment may possess anti-inflammatory, insulin-inhibitory, analgesic and antipyretic activities. It was found that synthesized compounds are likely to be low-toxic (class 4) and non-toxic (class 5).

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