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Isoxazolo[4,3-*e*]indazole as a new heterocyclic system: design, synthesis, spectroscopic characterization, and antibacterial activity

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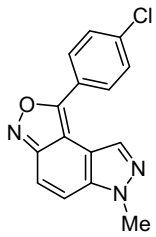
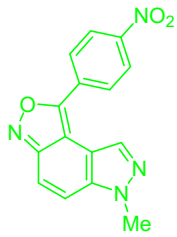


Antibacterial



Fluorescent

The new heterocyclic system isoxazolo[4,3-*e*]indazole was synthesized *via* the nucleophilic substitution of a hydrogen in 1-methyl-5-nitro-1*H*-indazole with different aryl acetonitriles in basic medium. The fluorescence properties and antibacterial activities of the new compounds against Gram-positive and Gram-negative bacterial species were also studied.

Keywords: indazole, isoxazole, antibacterial activity, emission and absorption spectra, fluorescence.

Heterocycles constitute the largest group of organic compounds and are becoming ever more significant in all aspects of pure and applied chemistry. Many natural products, such as hormones, vitamins, alkaloids, antibiotics, as well as pharmaceuticals, herbicides, dyes, and other products of technical importance (corrosion inhibitors, sensitizers, stabilizing agents, etc.) include heterocycles in their structure. Among numerous heterocycles, isoxazoles are an important class of heterocyclic pharmaceuticals and bioactive natural products because of their broad spectrum of biological activities, including potent and selective antagonism of the NMDA receptor[1] and antiHIV activity.[2]

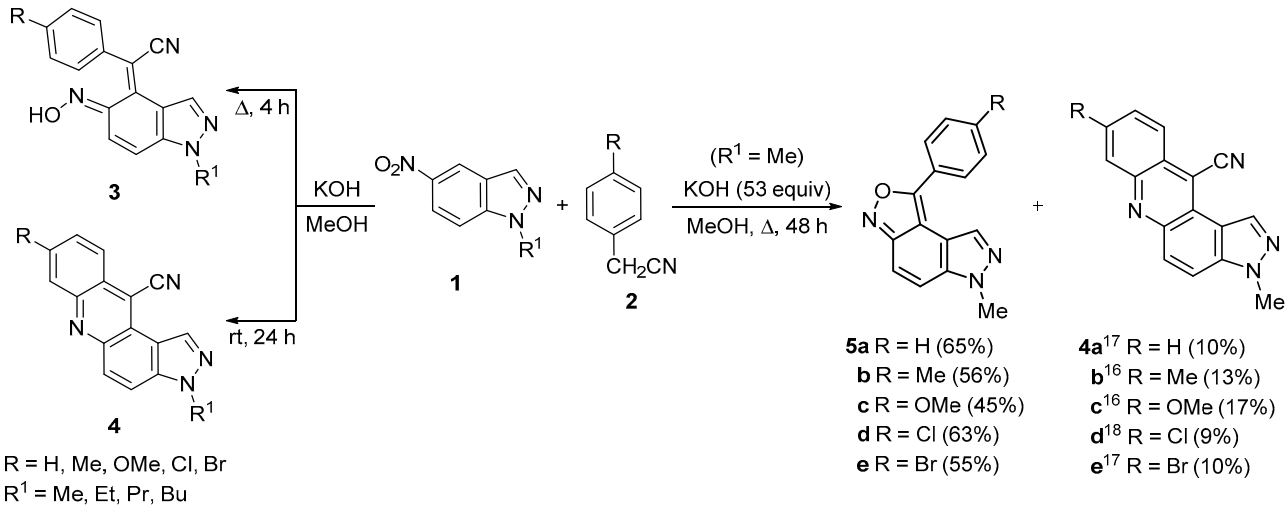
On the other hand, indazole derivatives exhibit interesting biological properties, such as antidepressant,[3] anti-inflammatory,[4,5] analgesic and antipyretic,[6] antidopaminergic,[7] antitumor,[8] anti-emetic,[9] and antiHIV activities.[10] In addition, indazole ring system is present in many other compounds, such as herbicides, dyes or sweeteners, as guanidine-1*H*-indazole.[11–13] Recently, indazole scaffold has become of interest as parent structure of dyes[14] and fluorescent substances.[15–18] A combination of the indazole moiety with the isoxazole nucleus may provide compounds with interesting optical and biological properties.

Taking into consideration the available literature data and in continuation of our studies on the synthesis of new biologically active[19–21] and fluorescent heterocyclic compounds,[15–18,22,23] we have synthesized a new heterocyclic system isoxazolo[4,3-*e*]indazole *via* the nucleophilic substitution of hydrogen[24] in 1-methyl-5-nitro-1*H*-indazole with various aryl acetonitriles in basic medium with the purpose to study spectral and fluorescence properties. Antibacterial activity of the obtained compounds against Gram-positive and Gram-negative bacterial species has been also studied.

Synthesis and structure of isoxazolo[4,3-*e*]indazoles. Previously, we attempted to obtain isoxazolo[4,3-*e*]-indazoles from the reaction of 1-alkyl-5-nitro-1*H*-indazoles **1**[25] with aryl acetonitriles **2** under different conditions. As we have reported, such reaction led to the formation of uncyclized green dyes 2-(1-alkyl-5-hydroxyimino-1,5-dihydro-4*H*-indazolylidene)-2-arylacetonitriles **3**[14] and fluorescent pyrazolo[4,3-*a*]acridines **4**[16–18] under reflux and room temperature conditions, respectively (Scheme 1).

In the current work, we found out that the best method for the synthesis of isoxazolo[4,3-*e*]indazoles **5a**–**e**, producing 45–65% yields, was the reaction of 1-methyl-5-nitro-1*H*-indazole **1** (R^1 = Me) with different aryl acetonitriles **2** in saturated KOH solution in MeOH at reflux for 48 h (Scheme 1). As by-products, pyrazolo[4,3-*a*]acridines **4a**–**e** were obtained in 9–17% yields. The work-up procedure and isolation of compounds **5a**–**e** and **4a**–**e**, which turned out to be very simple, were performed by filtration of the

Scheme 1

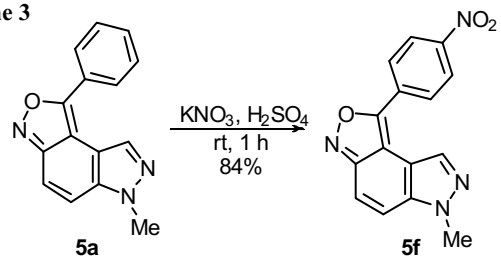


precipitated product after the neutralization of the reaction mixture with dilute HCl solution and washing the crude precipitate with cold acetone. Compounds **5a**–**e** are quite soluble in acetone, and the removal of the solvent from the filtrate and then recrystallization from MeOH give pure products **5a**–**e** while pyrazolo[4,3-*a*]acridines **4a**–**e** are nearly insoluble in cold acetone and remain in the precipitate.

A proposed mechanism to explain the formation of compounds **5a**–**e** and **4a**–**e** is shown in Scheme 2.[26] The different result with respect to the previously reported[14,16–18] is likely caused by the different conditions (refluxing the reaction mixture in combination with the high concentration of KOH), which leads to the preferential transformation of intermediate **A** into anion **B**, the precursor to isoxazolo[4,3-*e*]indazoles **5a**–**e** as the major products. The pathway from intermediate **A** through compound **3** is disfavored and results in formation of pyrazolo[4,3-*a*]-acridines **4a**–**e** as the minor products (yields 9–17%) (Scheme 2).

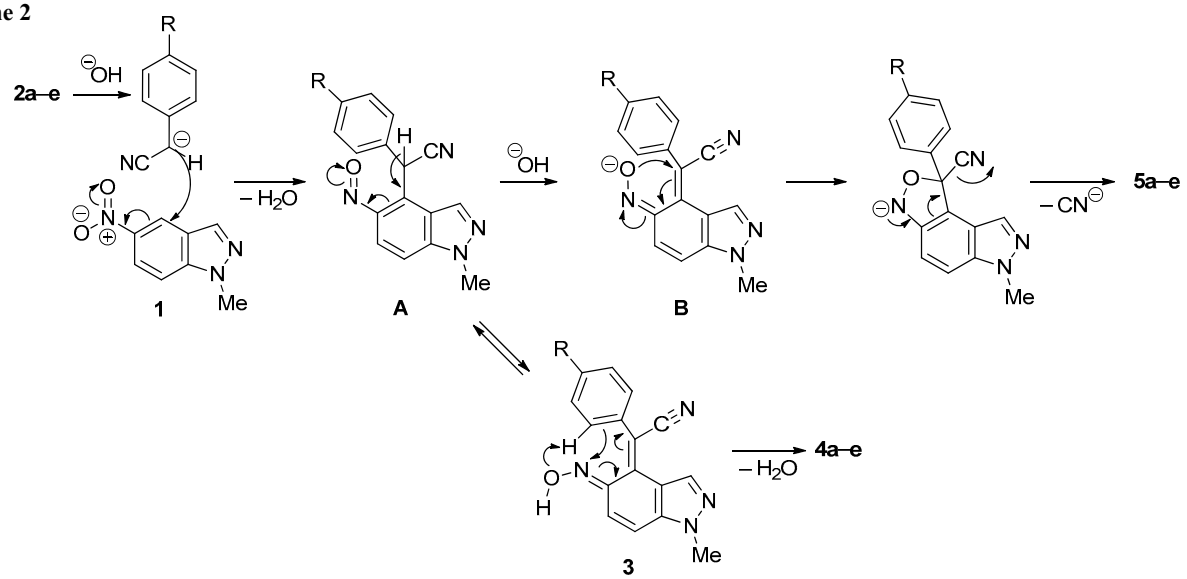
When R is an electron-withdrawing group such as NO_2 group, the yield of the reaction is very low because the corresponding conjugated base is a weak nucleophile. However, the nitration of compound **5a** with a mixture of sulfuric acid and potassium nitrate led to the formation of compound **5f** by the introduction of nitro group at the *para* position of the phenyl ring (Scheme 3).

Scheme 3



Structural assignments of the new compounds **5a**–**f** were based on their spectral and microanalytical data. For example, in the aromatic region of the ^{1}H NMR spectrum

Scheme 2



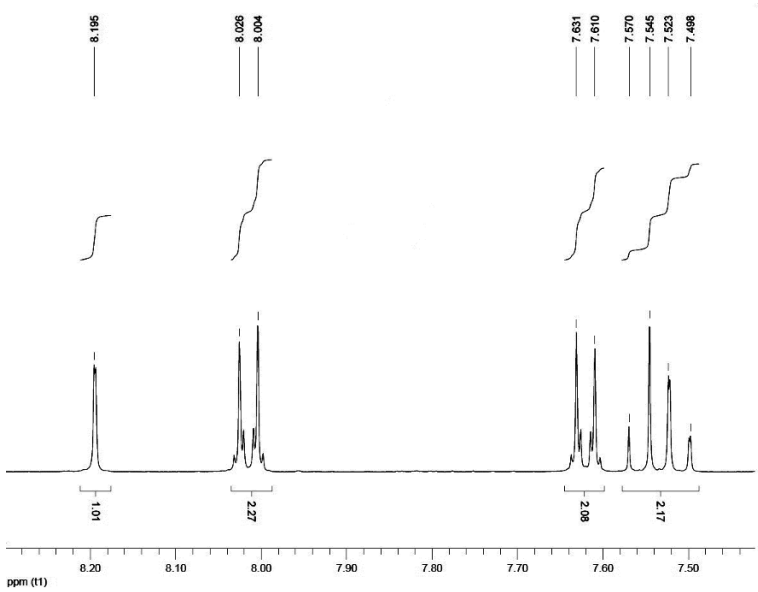


Figure 1. The expanded ^{1}H NMR spectrum of compound **5d** in downfield region.

of compound **5d**, there are two signals of an AA'BB' system at 8.01 and 7.62 ppm attributed to four aromatic protons of the 4-chlorophenyl ring and two doublet signals at 7.56 and 7.50 ppm assigned to two aromatic protons in the C-4 and C-5 positions, as well as a singlet signal at 8.20 ppm linked to the proton of the pyrazole ring (Fig. 1). The ^{1}H NMR spectra of the corresponding open-chain compounds **3** are markedly different (Supplementary information Fig. S1 and S2). Also there are 13 different carbon atom signals in the ^{13}C NMR spectrum of compound **5d**. All this evidence taken in conjunction with molecular ion peak at *m*/*z* 283 $[M(^{35}Cl)]^{+}$ supports the tricyclic structure of compound **5d**. The products **4a**–**e** were characterized by comparison of their spectroscopic and physical data with those of samples synthesized by the procedure given in the literature[16–18] (Supplementary information).

Photophysical properties of compounds 5a–**f**. Compounds **5a**–**f** were spectrally characterized by UV-Vis and fluorescence spectroscopy in the wavelength range of 200–1000 nm. The emission spectra of compounds **5a**–**e** did not show any fluorescence emission peak even at high concentrations while compound **5f** produced fluorescence at concentration 1×10^{-4} mol/l in chloroform allowing to investigate its solvatochromic properties in different solvents (Table 1, Fig. 2). The fluorescence absorption and emission bands of compound **5f** undergo a bathochromic shift with increasing polarity of solvent. Increasing the solvent polarity stabilizes the excited state of the molecule relative to the ground state causing the experimentally observed red shift of the absorption maximum (Table 1). For example, in the absorption and emission spectra of compound **5f**, the maxima of the absorption (λ_{abs}) and emission (λ_{flu}) spectra shift from 405 to 430 nm and 455 to 560 nm, respectively, as the solvent changes from cyclohexane to MeOH (Table 1).

The values of extinction coefficient (ε) were calculated as the slope of the plot of absorbance *vs* concentration. The fluorescence quantum yield of compound **5f** was determined *via* comparison methods, using fluorescein as a standard sample in 0.1 M NaOH and MeOH solution.[27] The used value of the fluorescein emission quantum yield is 0.79, and the obtained emission quantum yield of the compound **5f** is 0.29.

The absorption band of compound **5f** with λ_{abs} 405–430 nm in different solvents can be attributed to π–π* transition from the electron-donating (N-6 atom) to electron-accepting groups (nitro group). The fluorescence emission of the new compound **5f** can be explained in terms of the extended conjugation pathway.[15–18] Comparing the resonance structures of compounds **5a**–**e** and **5f** demonstrates that π-electron delocalization in compound **5f** can occur much more easily than in compounds **5a**–**e**.

Antibacterial studies of compounds 5a–f. The antibacterial activity of compounds **5a**–**f** was tested against two standard strains of Gram-positive (*Staphylococcus aureus* ATCC 29213 and *Bacillus subtilis* ATCC 6633) and two strains of Gram-negative bacteria (*Escherichia coli* ATCC 10538 and *Salmonella typhimurium* ATCC 14028) species (Table 2), using the broth microdilution method as pre-

Table 1. Spectroscopic data for compound **5f** at 298 K in different solvents*

Solvent	λ_{abs}, nm	$\varepsilon \times 10^{-3}$, mol × l^{-1} × cm^{-1}	λ_{flu}, nm
MeOH	430	8.7	560
DMF	425	8.4	550
MeCN	420	7.3	545
Chloroform	420	6.0	505
1,4-Dioxane	415	6.4	495
Cyclohexane	405	5.0	455

* λ_{abs} – Absorption maximum wavelength, ε – extinction coefficient at λ_{abs}, λ_{flu} – fluorescence maximum wavelength with excitation at λ_{abs}.

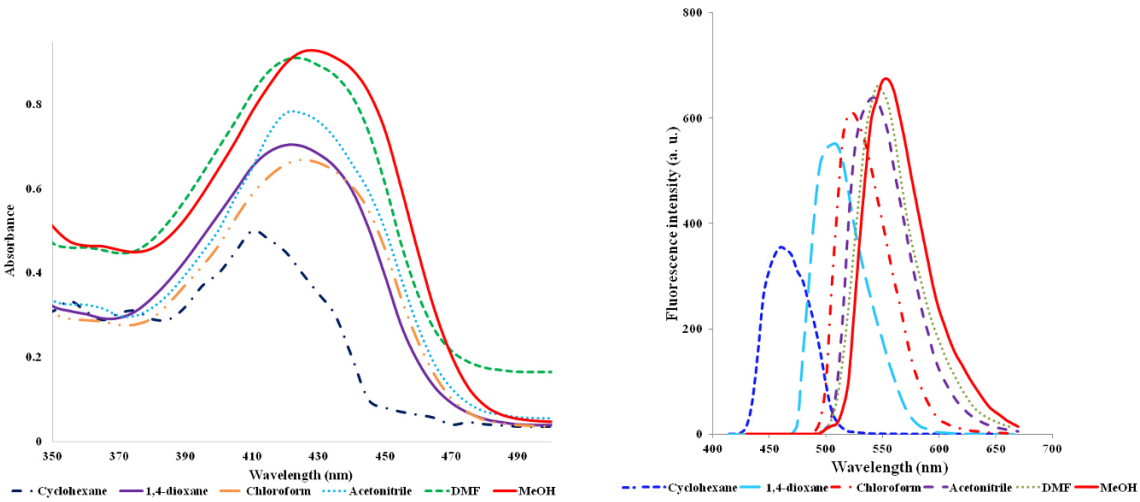


Figure 2. UV-Vis absorption spectra (left) (5×10^{-4} mol/l) and fluorescence emission spectra (right) (1×10^{-4} mol/l) of compound **5f** in different solvents with excitation at λ_{abs}.

viously described.[27] We used amoxicillin and ciprofloxacin as reference compounds in the evaluation of antibacterial activity. The lowest concentration of the antibacterial agent that prevents growth of the test organism, as detected by lack of visual turbidity (matching the negative growth control), is defined as the minimum inhibitory concentration (MIC). Experimental details of the tests can be found in our earlier study.[21]

The antibacterial tests performed on compounds **5a**–**f** confirmed that they were effective only against the two Gram-negative species. Also the test results revealed that compound **5d**, which has chlorine substituent, showed higher antibacterial activity against the *Escherichia coli* ATCC 10538 and *Salmonella typhimurium* ATCC 14028 species compared to the well-known antibacterial agent amoxicillin (Table 2). We propose that the chlorine substituent might change the binding characteristics of the ligand to their respective receptors and, thereby, improve the biological activity.

In conclusion, we have synthesized a new heterocyclic system isoxazolo[4,3-*e*]indazole *via* the nucleophilic substitution of hydrogen reaction of 1-methyl-5-nitro-1*H*-indazole with different aryl acetonitriles in saturated methanolic KOH solution at room temperature. Spectroscopic characterization, fluorescence properties, and antibacterial activity of the new compounds against Gram-positive and Gram-negative bacterial species were also studied. The results showed that the compound containing 4-nitrophenyl substituent produces fluorescence while the one with 4-chlorophenyl substituent shows the highest antibacterial activity among other synthesized compounds.

Experimental

Absorption and fluorescence spectra were recorded on a Varian 50-bio UV-Visible spectrophotometer and a Varian Cary Eclipse spectrofluorophotometer. UV–Vis and fluorescence scans were recorded from 200 to 1000 nm. All measurements were carried out at room temperature. IR (as KBr discs) spectra were obtained on a Tensor 27 spectrometer and only noteworthy absorptions are listed. ^{1}H and ^{13}C NMR spectra (400 and 100 MHz, respectively) were recorded on a Bruker Avance DRX-400 FT spectrometer in $CDCl_3$. Chemical shifts are reported in ppm downfield from TMS as internal standard. Electron impact ionization mass spectra were recorded on a Varian Mat CH-7 at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer. Melting points were measured on an Electrothermal type 9100 melting point apparatus.

Table 2. Antibacterial activity of compounds **5a**–**f** (MIC, μg/ml)

Compound	*Staphylococcus aureus* ATCC 29213	*Bacillus subtilis* ATCC 6633	*Escherichia coli* ATCC 10538	*Salmonella typhimurium* ATCC 14028
5a	–	–	75	50
5b	–	–	45	75
5c	–	–	35	50
5d	–	–	10	25
5e	–	–	45	65
5f	–	–	32	65
Ciprofloxacin	16	0.05	1	>128
Amoxicillin	25	0.06	150	>128

Amoxicillin, ciprofloxacin, and potassium hydroxide were purchased from Sigma–Aldrich. Other reagents and solvents were purchased from Merck. All solvents were dried according to standard procedures. Compound **1** was synthesized according to a literature procedure.[25] The microorganisms *Staphylococcus aureus* ATCC 29213, *Bacillus subtilis* ATCC 6633, *Escherichia coli* ATCC 10538, *Salmonella typhimurium* ATCC 14028 were purchased from the Pasteur Institute of Iran.

Synthesis of compounds 5a–e (General method). 1-Alkyl-5-nitro-1*H*-indazole **1** (1.77 g, 10 mmol) and nitrile **2a**–**e** (12 mmol) were added with stirring to a solution of KOH (30 g, 535 mmol) in methanol (70 ml). The mixture was refluxed for 48 h and then poured into water. The precipitate was filtered off, washed with water, and air-dried to give crude product **5a**–**e** with admixture of side product **4a**–**e**. Washing the crude product with acetone, evaporation of the filtrate, and recrystallization of the residue from MeOH gave pure compound **5a**–**e**, while crude compound **4a**–**e** remained as precipitate on the filter. Compound **4a**–**e** was purified by recrystallization from EtOH.

6-Methyl-1-phenyl-6*H*-isoxazolo[4,3-*e*]indazole (5a). Pale-yellow crystals (MeOH), mp 155–157°C. IR spectrum, ν, cm^{-1}: 3101, 3043 and 3007 (C–H Ar); 2958 (C–H); 1643, 1553 (C=C Ar). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.25 (3H, s, NCH_3); 7.56 (1H, d, *J* = 9.6, H Ar); 7.64 (1H, d, *J* = 9.6, H Ar); 7.75–7.86 (5H, m, H Ar); 8.24 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 37.5 (NCH_3); 106.1; 111.5; 115.2; 117.0; 124.9; 125.2; 128.1; 133.6; 137.3; 140.3; 157.3; 163.3 (C-1). Mass spectrum, *m*/*z* (I_{rel}, %): 249 $[M]^+$ (1), 248 (5), 235 (19), 158 (11), 119 (25), 91 $[C_7H_7]^+$ (100). Found, %: C 71.94; H 4.41; N 16.65. $C_{15}H_{11}N_3O$. Calculated, %: C 72.28; H 4.45; N 16.86.

6-Methyl-1-(*p*-tolyl)-6*H*-isoxazolo[4,3-*e*]indazole (5b). Pale-yellow crystals (MeOH), mp 181–183°C. IR spectrum, ν, cm^{-1}: 3095, 3041 and 3005 (C–H Ar); 2957 (C–H); 1638, 1557 (C=C Ar). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.51 (3H, s, CH_3); 4.16 (3H, s, N–CH_3); 7.44 (2H, d, *J* = 8.1, H Ar); 7.47 (1H, d, *J* = 9.6, H Ar); 7.54 (1H, d, *J* = 9.6, H Ar); 7.97 (2H, d, *J* = 8.1, H Ar); 8.21 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.6 (CH_3); 36.4 (NCH_3); 106.8; 111.8; 115.4; 117.4; 125.8; 126.8; 129.9; 132.6; 137.3; 140.4; 157.3; 163.0 (C-1). Mass spectrum, *m*/*z* (I_{rel}, %): 263 $[M]^+$ (1), 262 (3), 249 (21), 235 (23), 234 (31), 91 $[C_7H_7]^+$ (100). Found, %: C 72.78; H 4.95; N 16.11. $C_{16}H_{13}N_3O$. Calculated, %: C 72.99; H 4.98; N 15.96.

1-(4-Methoxyphenyl)-6-methyl-6*H*-isoxazolo[4,3-*e*]indazole (5c). Pale-yellow crystals (MeOH), mp 193–195°C. IR spectrum, ν, cm^{-1}: 3103, 3043 and 3000 (C–H Ar); 2953 (C–H); 1648, 1555 (C=C Ar). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.93 (3H, s, OCH_3); 4.07 (3H, s, N–CH_3); 7.15 (2H, d, *J* = 8.6, H Ar); 7.55 (1H, d, *J* = 9.6, H Ar); 7.60 (1H, d, *J* = 9.6, H Ar); 7.72 (2H, d, *J* = 8.6, H Ar); 8.16 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 35.0 (NCH_3); 56.4 (O-CH_3); 108.3; 112.1; 114.4; 115.4; 117.9; 125.1; 132.9; 137.1; 140.9; 155.5; 159.7; 163.8 (C-1). Mass spectrum, *m*/*z* (I_{rel}, %): 279 $[M]^+$ (3), 278 (7), 264 (31), 250 (25), 235 (14), 91 $[C_7H_7]^+$ (100). Found, %: C 68.70; H 4.67; N 14.93. $C_{16}H_{13}N_3O_2$. Calculated, %: C 68.81; H 4.69; N 15.05.

1-(4-Chlorophenyl)-6-methyl-6*H*-isoxazolo[4,3-*e*]indazole (5d). Pale-yellow crystals (EtOH), mp 147–149°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.05 (3H, s, N–CH_3); 7.50 (1H, d, *J* = 10.0, H Ar); 7.56 (1H, d, *J* = 10.0, H Ar); 7.62 (2H, d, *J* = 8.8, H Ar); 8.01 (2H, d, *J* = 8.8, H Ar); 8.20 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 35.7 (NCH_3); 107.4; 112.3; 114.6; 117.2; 117.7; 125.2; 129.8; 134.1; 137.3; 141.4; 155.3; 163.5 (C-1). Mass spectrum, *m*/*z* (I_{rel}, %): 285 $[M(^{37}Cl)]^+$ (1), 283 $[M(^{35}Cl)]^+$ (3), 249 (17), 235 (21), 234 (35), 91 $[C_7H_7]^+$ (100). Found, %: C 63.29; H 3.52; N 14.99. $C_{15}H_{10}ClN_3O$. Calculated, %: C 63.50; H 3.55; N 14.81.

1-(4-Bromophenyl)-6-methyl-6*H*-isoxazolo[4,3-*e*]indazole (5e). Pale-yellow crystals (EtOH), mp 153–155°C. IR spectrum, ν, cm^{-1}: 3105, 3049 and 3004 (C–H Ar); 2956 (C–H); 1643, 1559 (C=C Ar). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.09 (3H, s, N–CH_3); 7.55 (1H, d, *J* = 9.8, H Ar); 7.62 (1H, d, *J* = 9.8, H Ar); 7.68 (2H, d, *J* = 8.6, H Ar); 8.15 (2H, d, *J* = 8.6, H Ar); 8.19 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.1 (NCH_3); 108.8; 112.5; 114.5; 117.9; 118.8; 123.8; 127.3; 132.9; 134.9; 141.0; 155.5; 163.9 (C-1). Mass spectrum, *m*/*z* (I_{rel}, %): 329 $[M(^{81}Br)]^+$ (6), 327 $[M(^{79}Br)]^+$ (7), 249 (15), 234 (21), 91 $[C_7H_7]^+$ (100). Found, %: C 54.78; H 3.06; N 12.73. $C_{15}H_{10}BrN_3O$. Calculated, %: C 54.90; H 3.07; N 12.80.

3-Methyl-3*H*-pyrazolo[4,3-*a*]acridine-11-carbonitrile (4a). Shiny yellow needles, mp 250–253°C (EtOH) (mp 251–253°C[17]).

3,8-Dimethyl-3*H*-pyrazolo[4,3-*a*]acridine-11-carbonitrile (4b). Shiny yellow needles, mp 263–265°C (EtOH) (mp 261–264°C[16]).

8-Methoxy-3-methyl-3*H*-pyrazolo[4,3-*a*]acridine-11-carbonitrile (4c). Shiny yellow needles, mp 323–325°C (EtOH) (mp 325–327°C[16]).

8-Chloro-3-methyl-3*H*-pyrazolo[4,3-*a*]acridine-11-carbonitrile (4d). Shiny yellow needles, mp 232–235°C (EtOH) (mp 231–233°C[18]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.25 (3H, s, CH_3); 7.78 (1H, dd, *J* = 8.8, *J* = 2.0, H Ar); 7.93 (1H, d, *J* = 9.2, H Ar); 8.07 (1H, d, *J* = 9.2, H Ar); 8.35 (1H, d, *J* = 1.5, H Ar); 8.39 (1H, d, *J* = 8.8, H Ar); 9.19 (1H, s, H Ar).

8-Bromo-3-methyl-3*H*-pyrazolo[4,3-*a*]acridine-11-carbonitrile (4e). Shiny yellow needles, mp 268–270°C (EtOH) (mp 266–268°C[17]).

6-Methyl-1-(4-nitrophenyl)-6*H*-isoxazolo[4,3-*e*]indazole (5f). Potassium nitrate (0.71 g, 7 mmol) dissolved in concentrated sulfuric acid (2 ml) was added with stirring to a solution of compound **5a** (1.2 g, 5 mmol) in concentrated sulfuric acid (4 ml) over 30 min at 0–5°C. After the addition was completed, the mixture was allowed to warm to room temperature while stirring for 30 min. After pouring this mixture onto crushed ice and water (200 ml), the solid that precipitated was removed by filtration, washed with water, and dried to give crude product that was recrystallized from MeOH. Shiny yellow crystals, mp 250–252°C. IR spectrum, ν, cm^{-1}: 1345, 1540 (NO_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.18 (3H, s, NCH_3);

7.52 (1H, d, J = 9.6, H Ar); 7.59 (1H, d, J = 9.6, H Ar); 8.22 (1H, s, H Ar); 8.24 (2H, d, J = 8.7, H Ar); 8.49 (2H, d, J = 8.7, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.7 (NCH_3); 109.3; 112.1; 114.5; 119.3; 119.9; 124.0; 129.7; 133.4; 139.4; 148.0; 155.3; 162.2 (C-1). Mass spectrum, m/z (I_{rel}, %): 294 $[M]^+$ (2), 280 (15), 249 (9), 235 (18), 234 (37), 91 $[C_7H_7]^+$ (100). Found, %: C 61.04; H 3.40; N 18.89. $C_{15}H_{10}N_4O_3$. Calculated, %: C 61.22; H 3.43; N 19.04.

Supplementary information file to this article containing selected ^{1}H and ^{13}C NMR spectra of the synthesized compounds is available online at http://link.springer.com/journal/10593.

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