Received: 30 March 2020 | Revised: 29 April 2020 | Accepted: 10 May 2020

DOI: 10.1002/jhet.4028

WILEY

ARTICLE

Synthesis of new-type 1,3,6-triazocine via intramolecular reactions of iodocyclization and [3+2] azido cycloaddition

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Abstract

Selective iodocyclization of 6-(alkenylamino)-1-allylpyrazolo[3,4-*d*]pyrimidines provided hydrogenated derivatives of 1-allyl-8(9)-iodomethylimidazo(pyrimido)[1,2-*a*]pyrazolo[4,3-*e*]pyrimidines which were further reacted with NaN_3 at 75°C to 80°C to give a series of new-type 1,3,6-triazocines annulated with the pyrazole, pyrimidine, imidazole (or pyrimidine), and 1,2,3-triazole rings. The compounds synthesized were structurally characterized by analytical, spectral (IR, ^1H and ^{13}C NMR, HPLC-mass), and X-ray diffraction data.

1 | INTRODUCTION

The literature on triheteroatomic eight-membered heterocycles mainly refers to ring structures with various combinations of nitrogen, oxygen, and sulfur atoms.[1] They are notable for their broad synthetic potential, peculiar structural features, and pronounced biological activity. A special place in this class of medium-sized heterocycles is occupied by triazocines which may be considered aza homologues of diazepines, well-known pharmacological agents.[2] However, triazocines have been much less studied, with few reported examples bearing nitrogen atoms at ring positions 1,2,4,[3–6] 1,2,5,[7–9] 1,3,5,[10–13] and 1,3,6.[14–20] Particularly worthy of attention are fused 1,3,6-triazocines some of which show promise as potential antiallergens,[14,15] anticonvulsants,[16] and HIV integrase inhibitors.[20] These compounds contain the 1,3,6-triazocine core annulated with the benzimidazole[14,15] or pyridotriazine ring,[20] or with the benzene, pyrrole, and pyrazole rings together.[16]

We find it challenging to develop a facile route to new polyheterocyclic systems in which the edges of the 1,3,6-triazocine core are fused the pyrazole, pyrimidine, imidazoline (or dihydropyrimidine), and 1,2,3-triazoline moieties. The synthetic strategy proposed in the present study is based on two intramolecular processes, electrophilic iodocyclization and the following [3+2] cycloaddition of the in situ generated azido function to the allyl double bond.

Iodine-mediated reactions of functional unsaturated compounds offer a powerful tool to efficiently construct various mono and fused heterocyclic molecules.[21,22] This promising field of reactions is exemplified by the

intramolecular iodocyclization of fused 2-(alkenylamino) pyrimidones which affords the corresponding iodomethyl-functionalized imidazo and pyrimido annulated cores[23–26]; the following nucleophilic substitution of the iodine atom leads to azidomethyl derivatives further converted to amines and 1,2,3-triazoles via cycloaddition reactions.[25] However, there is little available information on intramolecular azido-to-alkenyl [3+2] cycloadditions and mainly on those occurring in the benzene,[27] indole,[28] and azetidinone derivatives.[29] Here we aim to design the substrate molecules so that the azidomethyl and allyl groups undergoing cycloaddition are the substituents on different moieties of the fused polyheterocyclic core.

2 | RESULTS AND DISCUSSION

As key substrates for the intramolecular cyclizations to yield target polyheteroannulated 1,3,6-triazocines, we chose 6-(alkenylamino)-1-allyl-1,5-dihydro-4H-pyrazolo [3,4-*d*]pyrimidin-4-ones **4a-e** (Scheme 1, Table 1) synthesized from the corresponding 6-chloro derivative **2** by reactions with allylamine **3a**, *N*-methylallylamine **3b**, diallylamine **3c**, 2-methylprop-2-en-1-amine **3d**, and but-3-en-1-amine **3e**. In turn, compound **2** was obtained by alkaline hydrolysis of 1-allyl-4,6-dichloro-1*H*-pyrazolo [3,4-*d*]pyrimidine **1** which resulted from the cyclocondensation of 2,4,6-trichloropyrimidine-5-carbaldehyde[30] with allylhydrazine.

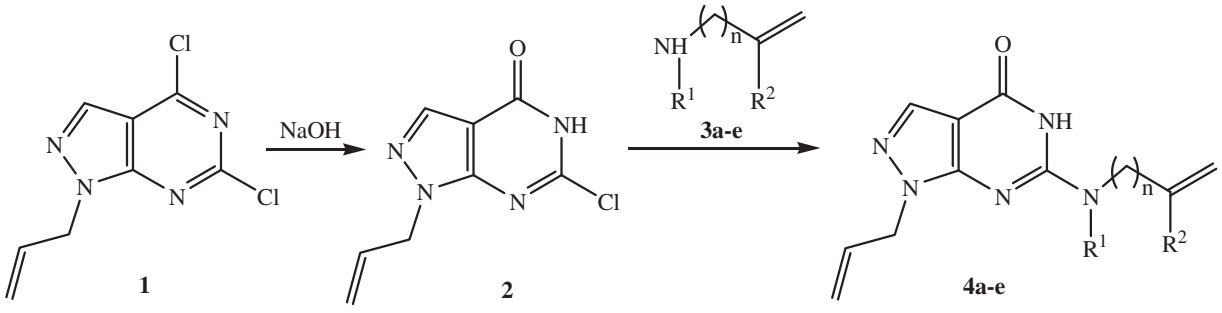
Pyrazolopyrimidones **4a-e** contain two alkene sites which can potentially be attacked by electrophilic reagents, with the double bond in the alkenylamino moiety appearing more reactive. As an example, the reaction of compound **4a** with a 3-fold excess of iodine in acetic acid involves only the 6-alkenylamino substituent and proceeds as an intramolecular iodocyclization to give salt-like pentaiodide **5a** which is almost quantitatively isolated from the reaction mixture in an analytically pure state. By treating this product with Na_2SO_3 in acetone, it is converted to 1-allyl-8-iodomethyl-7,8-dihydro-1H-imidazo[1,2-*a*]pyrazolo[4,3-*e*]pyrimidin-4(6H)-one **6a** in 86% yield. The iodine-induced cyclization of 6-alkenylamino derivatives **4b-e** into pentaiodides **5b-e** proceeds likewise in 92% to 99% yields. Bases **6c,e** are obtained in the same way as **6a**, whereas their analogues **6b,d** turn out to more efficiently result from the treatment of salts **5b,d** with the equivalent amount of NaI and AcONa (Scheme 2).

The angular structure of tricyclic fused heterocycles **6a-e** which implies the presence of the conjugated bonds O═C—N═C < in the pyrimidone ring is supported by the reduced frequencies (1646-1651 cm^{-1}) of the carbonyl stretching vibrations in the IR spectra. The ^{13}C NMR chemical shift of the carbonyl carbon atom is observed to be 163 to 167 ppm.[24]

As the next step in the design of target molecules, we converted iodine-containing heterocycles **6a-e** to the corresponding azido derivatives **7** which then spontaneously cyclized in situ (Scheme 3). As established in the study of this reaction, all mentioned substrates in DMF solution are inert towards NaN_3 at room temperature but **6a-e** enter into the reaction on heating the reaction mixture to 75°C to 80°C. Finally, intermediates **7a-e** undergo the intramolecular [3+2] cycloaddition of the azido function to the allyl double bond to produce new-type polyheteroannulated[1,2,3]triazolo[5,1-*e*][1,3,6]triazocines **8a-e** in 67% to 91% isolated yield.

The structure of the newly synthesized fused polyheterocyclic systems **8a-e** correlates well to their measured physicochemical parameters, with the most reliable structural characterization provided by the X-ray diffraction study of compound **8a** (see Experimental) (Figure 1).

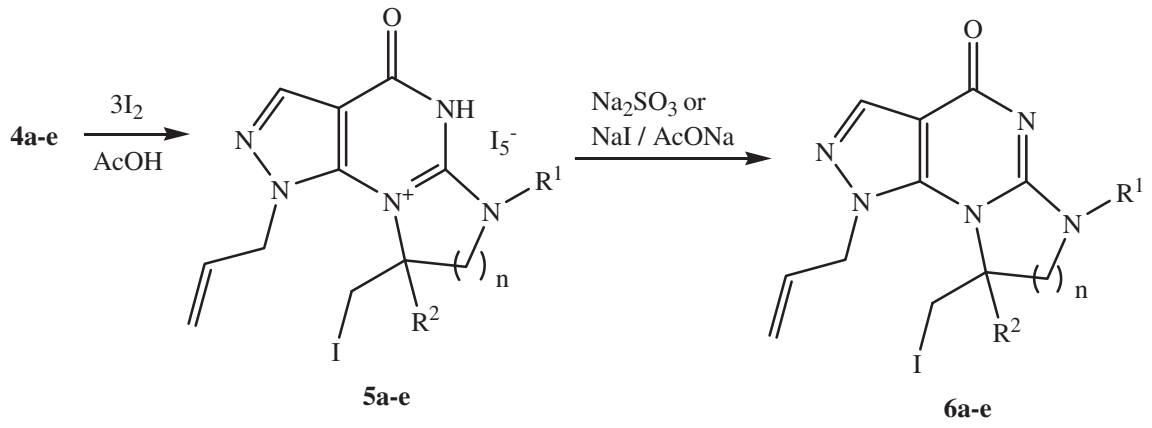
Structural parameters for **8a** (bond distances and angles) are as expected and in acceptable agreement with the structural formula of the compound. For example geometric parameters for atoms in heterocyclic system N1—N5; C1—C5 are typical for conjugated systems, thus bond lengths have intermediate values between single and double C—C, C—N and N—N bonds. The atoms



SCHEME 1 Synthesis of 6-(alkenylamino)-1-allyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-ones **4a-e**

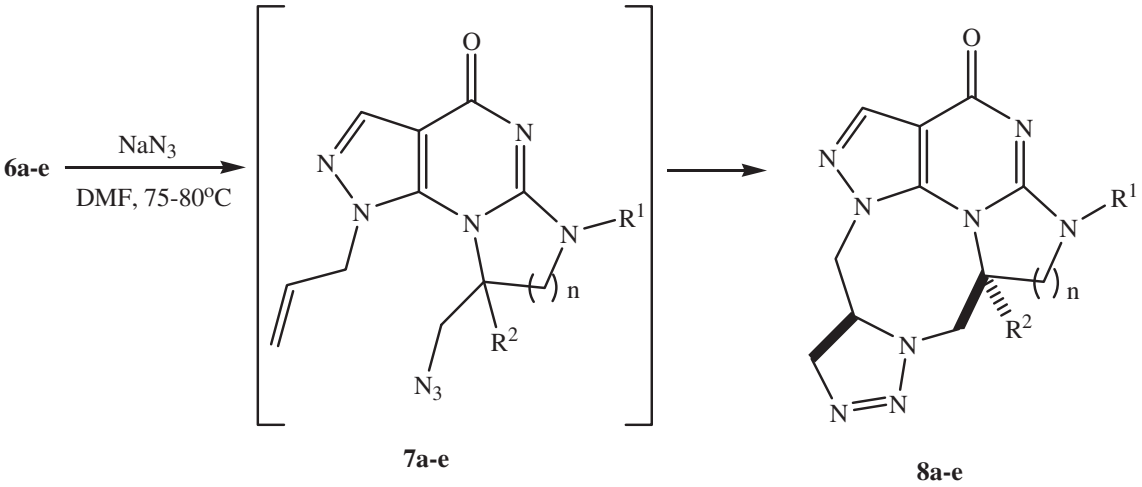
TABLE 1 Yields of products **4a-e**, **5a-e**, **6a-e, 8a-e**

Entry	Product	n	R^1	R^2	Yield (%)
1	**4a**	1	H	H	78
2	**4b**	1	CH_3	H	98
3	**4c**	1	CH_2—CH═CH_2	H	67
4	**4d**	1	H	CH_3	92
5	**4e**	2	H	H	74
6	**5a**	1	H	H	95
7	**5b**	1	CH_3	H	99
8	**5c**	1	CH_2—CH═CH_2	H	99
9	**5d**	1	H	CH_3	94
10	**5e**	2	H	H	92
11	**6a**	1	H	H	86
12	**6b**	1	CH_3	H	81
13	**6c**	1	CH_2—CH═CH_2	H	84
14	**6d**	1	H	CH_3	79
15	**6e**	2	H	H	74
16	**8a**	1	H	H	91
17	**8b**	1	CH_3	H	85
18	**8c**	1	CH_2—CH═CH_2	H	81
19	**8d**	1	H	CH_3	67
20	**8e**	2	H	H	74



SCHEME 2 Synthesis of iodomethyl substituted compounds **5a-e** and **6a-e**

N1—N5 and C1—C6 located in the plane with rms deviation of fitted atoms of 0.040 and atom C7 has deviation from that plane for 0.172(4)Å, thus the corresponding dihedral angles N4C4N5C7, N3C4N5C7, C7C6N3C3 and C7C6N3C4 are −168.9(3), 10.9(3), 177.5(3) and −16.0(3)° respectively. The five membered cycle N6N7N8C10C11 is non-planar with maximum deviation atoms of 0.100(2)Å and it has envelope conformation with dihedral angle between planes N6N7N8C11 and N6C10C11 of 16.3(3)°. The eight-membered ring in the compound **8a** adopts a non-planar conformation, as expected, and it has wrap around conformation. All atoms of the eight-membered ring lie in three (I-III) planes N2N3C3C6C9, C6C8C9C10, N6C8C10, and rms deviation of fitted atoms in corresponding planes of 0.0245, 0.0220 and 0.0. The dihedral angles between least-squares planes I-II and II-III are 66.0(1)° and 54.1(3)° respectively. The conformation of eight-membered ring are shown on Figure 2.



SCHEME 3 Synthesis of polyheteroannulated 1,3,6-triazocines **8a-e**

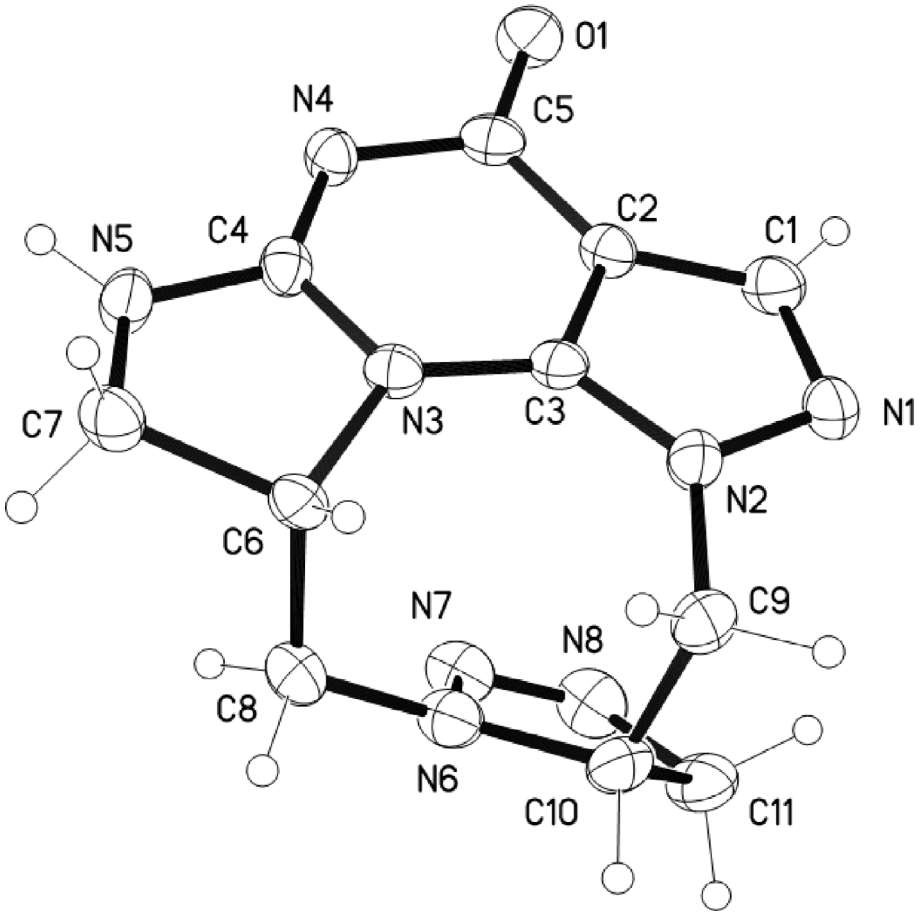


FIGURE 1 Molecular structure of **8a**. Thermal ellipsoids are drawn at 50% probability level

3 | CONCLUSION

We have developed an efficient access to new-type 1,3,6-triazocine scaffolds annulated with four, five- and six-membered heterocyclic systems. The proposed strategy involves, as key steps, two successive intramolecular conversions of 6-(alkenylamino)-1-allylpyrazolo[3,4-*d*]pyrimidines, viz., iodocyclization and azido-to-allyl [3+2] cycloaddition.

4 | EXPERIMENTAL

The starting material, 2,4,6-trichloropyrimidine-5-carbaldehyde, was prepared by the literature procedure.[30] The IR spectra of the compounds obtained were recorded on a Bruker Vertex 70 spectrometer in KBr pellets. The ^{1}H and ^{13}C NMR spectra were acquired on a Varian VXR-400 (400 and 100 MHz, respectively), Bruker

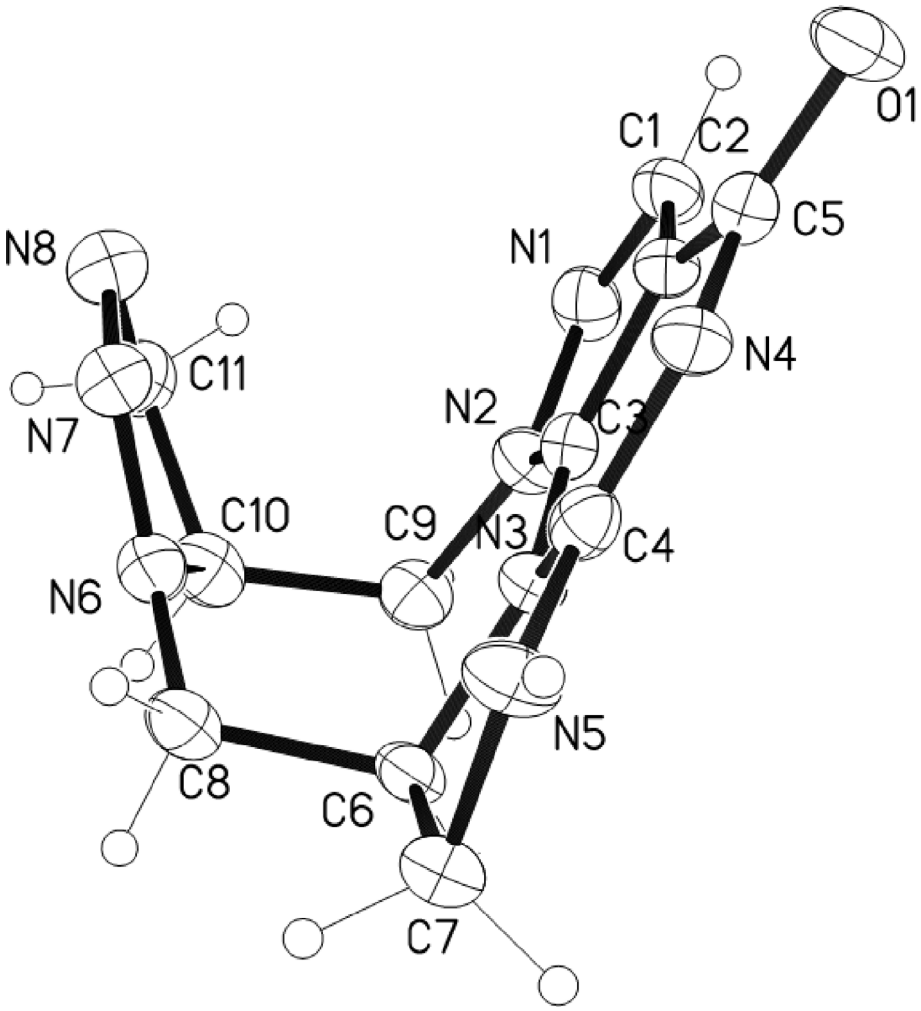


FIGURE 2 Conformation of eight-membered cycle in compound **8a**. Thermal ellipsoids are drawn at 50% probability level

Avance 500 (500 and 125 MHz respectively) and Bruker Avance 600 (600 and 150 MHz respectively) instrument in DMSO-d_6 solutions, with TMS as internal standard. The LC/MS spectra were recorded on an Agilent 1100 Series high-performance liquid chromatograph interfaced with an Agilent G1956B single quadrupole mass spectrometer.

4.1 | 4,6-Dichloro-1-(prop-2-enyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (1)

To a stirred solution of 2,4,6-trichloropyrimidine-5-carbaldehyde (25.32 g, 0.12 mol) in methanol (200 mL) was added at −20°C allylhydrazine obtained from the corresponding dihydrochloride (17.4 g, 0.12 mol) and triethylamine (36.4 g, 0.36 mol) in methanol (250 mL). The mixture was stirred at −20°C for 1 hour and then at 0°C for 2 hours, followed by standing at 0°C overnight. Methanol was removed and the residue was extracted with ethyl acetate (400 mL), evaporated, and purified by flash chromatography with chloroform as eluent. Yield 19.51 g (71%). The physicochemical characteristics of the product are as previously reported.[31]

4.2 | 6-Chloro-1-(prop-2-enyl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (2)

To a 135°C to 140°C heated solution of NaOH (20 g, 0.5 mol) in water (200 mL), compound **1** (20 g, 0.087 mol) was added and boiled until completely dissolved. Then activated carbon (1 g) was added to the reaction mixture, followed by boiling it for another 10 minutes, cooling to 40°C to 60°C, and filtering off the carbon. The filtrate was acidified with concentrated acetic acid to pH 3 to 4 and the resulting precipitate was filtered off, washed with water (50 mL), and dried at 70°C. Light yellow solid, yield: 89%; m.p. 196°C to 197°C; IR (KBr) ν_{max} (cm^{-1}): 3090 (NH stretching), 2873 (CH stretching), 1718 (C═O stretching), 1581 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.86 (d, J = 5.2 Hz, 2H, CH_2), 5.02 (d, J = 18.4 Hz, 1H, ═CH), 5.18 (d, J = 9.2 Hz, 1H, ═CH),

5.95 to 6.02 (m, 1H, =CH), 8.10 (s, 1H, CH pyrazole), 13.12 to 13.37 (m, 1H, NH); MS: m/z 211 (M + H); Anal. Calcd for $C_8H_7ClN_4O$: C, 45.62; H, 3.35; Cl, 16.83; N, 26.60; found: C, 45.56; H, 3.24; Cl, 16.77; N, 25.95.

4.3 | General procedure for the synthesis of compounds (4a-e)

A mixture of compound **2** (5.27 g, 25 mmol), amine **3a-d** (25 mmol) or amine hydrochloride **3e** (2.69 g, 25 mmol), and triethylamine (2.53 g, 25 mmol or 5.06 g, 50 mmol for **3e**) was boiled in ethanol (100 mL) for 4 hours. After the solvent was removed, water (50 mL) was added to the residue. The resulting solid precipitate was filtered off, washed with 5°C cooled ethanol (10 mL) and diethyl ether (10 mL), and purified by recrystallization from ethanol.

4.3.1 | 1-(Prop-2-enyl)-6-(prop-2-enylamino)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (4a)

White solid, m.p. 178°C to 179°C; IR (KBr) ν_{max} (cm^{-1}): 3393 (NH stretching), 2843 (CH stretching), 1699 (C=O stretching), 1618 (C=N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.95 (t, J = 5.6 Hz, 2H, CH_2), 4.70 (d, J = 5.2 Hz, 2H, CH_2), 5.02 (dd, J^1 = 16.8 Hz, J^2 = 1.6 Hz, 1H, =CH), 5.13 (dd, J^1 = 10.4 Hz, J^2 = 1.6 Hz, 2H, 2 =CH), 5.22 (dd, J^1 = 17.2 Hz, J^2 = 2.0 Hz, 1H, =CH), 5.87 to 6.00 (m, 1H, =CH), 6.64 to 6.71 (m, 1H, NH), 7.78 (s, 1H, CH pyrazole), 10.48 to 10.51 (m, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): δ 43.0, 48.8, 100.0, 116.2, 117.6, 133.8, 134.8, 135.2, 153.8, 154.5, 158.2; MS: m/z 232 (M + H); Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.67; N, 30.28; found: C, 57.06; H, 5.62; N, 30.25.

4.3.2 | 6-[Methyl(prop-2-enyl)amino]-1-(prop-2-enyl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (4b)

White solid, m.p. 143°C to 145°C; IR (KBr) ν_{max} (cm^{-1}): 3202 (NH stretching), 2934 (CH stretching), 1674 (C=O stretching), 1591 (C=N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.04 (s, 3H, CH_3), 4.18 (d, J = 5.6 Hz, 2H, CH_2), 4.70 (d, J = 5.2 Hz, 2H, CH_2), 5.03 (d, J = 17.2 Hz, 1H, =CH), 5.13 to 5.18 (m, 3H, 3 =CH), 5.77 to 5.87 (m, 1H, =CH), 5.91 to 6.00 м (m, 1H, =CH), 7.79 (s, 1H, CH pyrazole), 10.66 to 10.69 (m, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 35.9, 48.8, 52.0; 99.2, 117.4, 117.6, 133.4, 133.9, 134.7, 153.8, 154.3, 159.0; MS: m/z 246 (M + H); Anal. Calcd for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55; found: C, 58.66; H, 6.13; N, 28.49.

4.3.3 | 6-(Diprop-2-enylamino)-1-(prop-2-enyl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (4c)

White solid, m.p. 119°C to 121°C; IR (KBr) ν_{max} (cm^{-1}): 3188 (NH stretching), 1675 (C=O stretching), 1571 (C=N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.15 (d, J = 4.8 Hz, 4H, $2CH_2$), 4.71 (d, J = 5.2 Hz, 2H, CH_2), 5.05 (d, J = 18.4 Hz, 1H, =CH), 5.14 to 5.20 (m, 5H, 5 =CH), 5.78 to 5.88 (m, 2H, 2 =CH), 5.91 to 6.01 (m, 1H, =CH), 7.79 (s, 1H, CH pyrazole), 10.59 to 10.62 (m, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): δ 48.9, 49.9, 99.3, 117.4, 117.7, 133.6, 133.8, 134.7, 153.2, 154.2, 158.9; MS: m/z 272 (M + H); Anal. Calcd for $C_{14}H_{17}N_5O$: C, 61.98; H, 6.32; N, 25.81; found: C, 61.89; H, 6.27; N, 25.80.

4.3.4 | 6-[(2-Methylprop-2-enyl)amino]-1-(prop-2-enyl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (4d)

White solid, m.p. 159°C to 161°C; IR (KBr) ν_{max} (cm^{-1}): 3395 (NH stretching), 2845 (CH stretching), 1692 (C=O stretching), 1619 (C=N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.72 (s, 3H, CH_3), 3.89 (d, J = 5.6 Hz, 2H, CH_2), 4.69 (d, J = 5.2 Hz, 2H, CH_2), 4.85 (d, J = 17.6 Hz, 2H, $=CH_2$), 5.04 (d, J = 17.2 Hz, 1H, =CH), 5.14 (d, J = 9.2 Hz, 1H, =CH), 5.90 to 6.03 (m, 1H, =CH), 6.67 to 6.73 (m, 1H, NH), 7.77 (s, 1H, CH pyrazole), 10.32 to 10.51 (m, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 20.8; 46.1, 48.9, 100.1, 110.9, 117.7, 133.9, 134.8, 142.6, 154.0, 154.6, 158.2; MS: m/z 246 (M + H); Anal. Calcd for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55; found: C, 58.68; H, 6.15; N, 28.52.

4.3.5 | 6-(But-3-enylamino)-1-(prop-2-enyl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (4e)

White solid, m.p. 143°C to 145°C; IR (KBr) ν_{max} (cm^{-1}): 3398 (NH stretching), 2847 (CH stretching), 1699 (C=O stretching), 1620 (C=N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.30 (q, J = 6.8 Hz, 2H, CH_2), 3.38 (q, J = 6.8 Hz, 2H, CH_2), 4.71 (d, J = 5.2 Hz, 2H, CH_2), 5.03 (d, J = 8.0 Hz, 1H, =CH), 5.06 to 5.16 (m, 3H, 3 =CH), 5.77 to 5.87 (m, 1H, =CH), 5.92 to 6.02 (m, 1H, =CH), 6.44 to 6.50 (m, 1H, NH), 7.75 (s, 1H, CH pyrazole), 10.39 to 10.41 (m, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ

33.4; 40.1, 48.8, 99.9, 117.2, 117.5, 133.9, 134.7, 136.2, 153.9, 154.6, 158.2; MS: m/z 246 (M + H); Anal. Calcd for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55; found: C, 58.72; H, 6.14; N, 28.54.

4.4 | General procedure for the synthesis of compounds (5a-e)

To a stirred solution of compound **4a-e** (9 mmol) in acetic acid (30 mL), a solution of iodine (6.86 g, 27 mmol) in acetic acid (300 mL) was slowly added. After 48 hours, the resulting salt-like precipitate was filtered off, washed with acetic acid (50 mL) and hexane (30 mL), and dried.

4.4.1 | 8-(Iodomethyl)-4-oxo-1-(prop-2-enyl)-1,4,5,6,7,8-hexahydroimidazo[1,2-*a*]pyrazolo[4,3-*e*]pyrimidin-9-ium pentaiodide (5a)

Braun solid, m.p. 173°C to 175°C; IR (KBr) ν_{max} (cm^{-1}): 1710 (C═O stretching), 1671 (C═N^+ stretching), 1587 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.56 to 3.59 (m, 1H, CH), 3.64 to 3.68 (m, 1H, CH), 3.72 to 3.74 (m, 1H, CH), 4.04 to 4.09 (m, 1H, CH), 4.87 (d, J = 21.0 Hz, 1H, ═CH), 5.06 (d, J = 20.4 Hz, 2H, CH_2), 5.32 (d, J = 11.2 Hz, 1H, ═CH), 5.35 to 5.36 (m, 1H, CH), 6.02 to 6.11 (m, 1H, ═CH), 8.17 (s, 1H, CH pyrazole); ^{13}C NMR (125 MHz, DMSO-d_6): δ 8.9, 49.7, 52.7, 58.5, 101.8, 118.5, 132.8, 138.1, 140.2, 153.4, 156.4; Anal. Calcd for $C_{11}H_{13}I_6N_5O$: C, 13.31; H, 1.32; I, 76.70; N, 7.05; found: C, 13.26; H, 1.29; I, 76.55; N, 7.02.

4.4.2 | 8-(Iodomethyl)-6-methyl-4-oxo-1-(prop-2-enyl)-1,4,5,6,7,8-hexahydroimidazo[1,2-*a*]pyrazolo[4,3-*e*]pyrimidin-9-ium pentaiodide (5b)

Braun solid, m.p. 172°C to 174°C; IR (KBr) ν_{max} (cm^{-1}): 1704 (C═O stretching), 1676 (C═N^+ stretching), 1585 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.15 (s, 3H, CH_3), 3.53 to 3.55 (m, 1H, CH), 3.60 to 3.63 (m, H, CH), 3.75 to 3.77 (m, H, CH), 4.09 to 4.14 (m, 1H, CH), 4.84 to 4.87 (m, 1H, CH), 5.00 to 5.07 (m, 2H, 2CH), 5.27 to 5.32 (m, 2H, 2CH), 6.01 to 6.11 (m, 1H, ═CH), 8.14 (s, 1H, CH pyrazole); ^{13}C NMR (125 MHz, DMSO-d_6): δ 8.3, 32.9, 52.6, 55.7, 57.0; 101.4, 118.3, 132.8, 137.8, 140.5, 152.9, 158.4; Anal. Calcd for $C_{12}H_{15}I_6N_5O$: C, 14.32; H, 1.50; I, 75.64; N, 6.96; found: C, 14.27; H, 1.47; I, 75.53; N, 6.87.

4.4.3 | 8-(Iodomethyl)-4-oxo-1,6-di(prop-2-enyl)-1,4,5,6,7,8-hexahydroimidazo[1,2-*a*]pyrazolo[4,3-*e*]pyrimidin-9-ium pentaiodide (5c)

Braun solid, m.p. 178°C to 180°C; IR (KBr) ν_{max} (cm^{-1}): 1703 (C═O stretching), 1660 (C═N^+ stretching), 1583 (C═N^+ stretching),; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.55 to 3.70 (m, 3H, 3CH), 4.04 to 4.09 (m, 1H, CH), 4.17 to 4.28 (m, 2H, 2CH), 4.83 to 4.88 (m, 1H, CH), 5.03 to 5.07 (m, 2H, 2CH), 5.28 (d, J = 10.0 Hz, 2H, 2 ═CH), 5.34 (d, J = 10.8 Hz, 1H, CH), 5.43 (d, J = 16.8 Hz, 1H, ═CH), 5.83 to 5.93 (m, 1H, CH), 6.02 to 6.11 (m, 1H, ═CH), 8.11 (s, 1H, CH pyrazole); ^{13}C NMR (150 MHz, DMSO-d_6): δ 8.6, 47.9, 52.7, 53.5, 57.0, 101.5, 118.5, 120.8, 130.4, 132.8, 137.8, 140.6, 152.6, 158.6; Anal. Calcd for $C_{14}H_{17}I_6N_5O$: C, 16.28; H, 1.66; I, 73.73; N, 6.78; found: C, 13.26; H, 1.29; I, 76.55; N, 7.02.

4.4.4 | 8-(Iodomethyl)-8-methyl-4-oxo-1-(prop-2-enyl)-1,4,5,6,7,8-hexahydroimidazo[1,2-*a*]pyrazolo[4,3-*e*]pyrimidin-9-ium pentaiodide (5d)

Braun solid, m.p. 143°C to 145°C; IR (KBr) ν_{max} (cm^{-1}): 3124 (NH stretching), 2886 (CH stretching), 1713 (C═O stretching), 1676 (C═N^+ stretching), 1580 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.01 (s, 3H, CH_3), 3.85 (q, J = 12.0 Hz, 2H, CH_2), 3.89 (s, 2H, CH_2), 4.81 (d, J = 17.6 Hz, 1H, ═CH), 5.25 to 5.28 (m, 2H, CH_2), 5.26 (d, J = 10.8 Hz, 1H, ═CH), 5.98 to 6.08 (m, 1H, ═CH), 8.22 (s, 1H, CH pyrazole); ^{13}C NMR (150 MHz, DMSO-d_6): δ 15.3, 25.6, 55.3, 57.7, 69.2; 103.0, 117.7, 132.8, 138.5, 140.9, 153.7, 156.6; Anal. Calcd for $C_{12}H_{15}I_6N_5O$: C, 14.32; H, 1.50; I, 75.64; N, 6.96; found: C, 14.29; H, 1.45; I, 75.58; N, 6.90.

4.4.5 | 9-(Iodomethyl)-4-oxo-1-(prop-2-enyl)-4,5,6,7,8,9-hexahydro-1*H*-pyrazolo[4,3-*e*]pyrimido[1,2-*a*]pyrimidin-10-ium pentaiodide (5e)

Braun solid, m.p. 126°C to 128°C; IR (KBr) ν_{max} (cm^{-1}): 3156 (NH stretching), 2956 (CH stretching), 1700 (C═O stretching), 1657 (C═N^+ stretching), 1599 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.16 to 2.25 (m, 1H, CH), 2.40 to 2.45 (m, 1H, CH), 3.46 to 3.55 (m, 2H, CH_2), 3.59 to 3.61 (m, 2H, CH_2), 4.84 to 4.90 (m, 1H, CH), 4.96 to 5.04 (m, 2H, CH_2), 5.21 to 5.26 (m, 1H, CH), 5.31 (d, J = 10.8 Hz, 1H, ═CH), 6.07 to 6.16 (m, 1H, ═CH), 8.15 (s, 1H, CH pyrazole); ^{13}C NMR (125 MHz,

DMSO-d_6): δ 4.7; 21.2; 35.1; 53.7, 54.9, 103.8, 117.9, 133.2, 136.9, 141.8, 148.9, 155.6; Anal. Calcd for $C_{12}H_{15}I_6N_5O$: C, 14.32; H, 1.50; I, 75.64; N, 6.96; found: C, 14.30; H, 1.49; I, 75.61; N, 6.95.

4.5 | General procedure for the synthesis of compounds (6a,c,e)

To a stirred solution of compound **5a,c,e** (7 mmol) in acetone (30 mL), Na_2SO_3 (1.76 g, 14 mmol) in water (20 mL) was added. After 2 hours, the resulting precipitate was filtered off, washed with water (20 mL), ethanol (5 mL), and hexane (20 mL), and then air-dried.

4.6 | General procedure for the synthesis of compounds (6b,d)

To a stirred solution of compound **5b,d** (7 mmol) in acetone (30 mL), NaI (1.20 g, 8 mmol) in acetone (30 mL) was added and the reaction mixture was stirred for 2 hours. The resulting precipitate was filtered off and dissolved in methanol (20 mL), followed by adding CH_3COONa (0.66 g, 8 mmol) to the stirred solution. After 8 hours, the solvent was distilled off and the solid residue was treated with water (20 mL), filtered off, and air-dried.

4.6.1 | 8-(Iodomethyl)-1-(prop-2-enyl)-7,8-dihydro-1*H*-imidazo[1,2-*a*]pyrazolo[4,3-*e*]pyrimidin-4(6*H*)-one (6a)

White solid, m.p. 145°C to 148°C; IR (KBr) ν_{max} (cm^{-1}): 3194 (NH stretching), 1646 (C═O stretching), 1599 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.43 to 3.58 (m, 3H, 3CH), 3.81 to 3.86 (m, 1H, CH), 4.78 (d, J = 17.2 Hz, 1H, ═CH), 4.95 (d, J = 16.8 Hz, 2H, CH_2), 5.05 to 5.08 (m, 1H, CH), 5.23 (d, J = 10.4 Hz, 1H, ═CH), 6.01 to 6.10 (m, 1H, ═CH), 7.78 (s, 1H, CH pyrazole), 8.41 to 8.48 (m, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 9.7, 46.6, 51.5, 56.0, 103.0, 117.1, 133.2, 136.3, 141.0, 157.3, 165.9; MS: m/z 358 (M + H); Anal. Calcd for $C_{11}H_{12}IN_5O$: C, 36.99; H, 3.39; I, 35.53; N, 19.61; found: C, 36.88; H, 3.36; I, 35.51; N, 19.57.

4.6.2 | 8-(Iodomethyl)-6-methyl-1-(prop-2-enyl)-7,8-dihydro-1*H*-imidazo[1,2-*a*]pyrazolo[4,3-*e*]pyrimidin-4(6*H*)-one (6b)

White solid, m.p. 179°C to 181°C; IR (KBr) ν_{max} (cm^{-1}): 1651 (C═O stretching), 1605 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.93 (s, 3H, CH_3), 3.44 to 3.46 (m, 1H, CH), 3.50 to 3.59 (m, 2H, CH_2), 3.88 to 3.93 (m, 1H, CH), 4.76 to 4.81 (m, 1H, CH), 4.91 to 5.03 (m, 3H, CH_2 + CH), 5.21 (d, J = 10.0 Hz, 1H, ═CH), 6.00 to 6.10 (m, 1H, ═CH), 7.79 (s, 1H, CH pyrazole); ^{13}C NMR (125 MHz, DMSO-d_6): δ 10.5, 31.5, 52.0, 53.4, 54.4, 103.3, 117.5, 133.7, 136.8, 141.6, 156.1, 166.3; MS: m/z 372 (M + H); Anal. Calcd for $C_{12}H_{14}IN_5O$: C, 38.83; H, 3.80; I, 34.19; N, 18.87; found: C, 38.78; H, 3.76; I, 34.15; N, 18.79.

4.6.3 | 8-(Iodomethyl)-1,6-di(prop-2-enyl)-7,8-dihydro-1*H*-imidazo[1,2-*a*]pyrazolo[4,3-*e*]pyrimidin-4(6*H*)-one (6c)

White solid, m.p. 180°C to 182°C; IR (KBr) ν_{max} (cm^{-1}): 1647 (C═O stretching), 1610 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.41 to 3.44 (m, 1H, CH), 3.52 to 3.60 (m, 2H, 2CH), 3.84 to 3.88 (m, 1H, CH), 3.96 to 4.09 (m, 2H, 2CH), 4.77 to 4.81 (m, 1H, CH), 4.94 to 4.98 (m, 2H, 2CH), 5.03 to 5.06 (m, 1H, CH), 5.21 to 5.26 (m, 2H, 2 ═CH), 5.33 (d, J = 17.2 Hz, 1H, ═CH), 5.81 to 5.90 (m, 1H, ═CH), 6.00 to 6.10 (m, 1H, ═CH), 7.80 (s, 1H, CH pyrazole); ^{13}C NMR (125 MHz, DMSO-d_6): δ 10.4, 47.0, 51.2, 52.1, 54.5, 103.7, 117.6, 119.0, 132.7, 133.7, 136.8, 141.6, 155.7, 166.2; MS: m/z 398 (M + H); Anal. Calcd for $C_{14}H_{16}IN_5O$: C, 42.33; H, 4.06; I, 31.95; N, 17.63; found: C, 42.19; H, 4.03; I, 31.87; N, 17.55.

4.6.4 | 8-(Iodomethyl)-8-methyl-1-(prop-2-enyl)-7,8-dihydro-1*H*-imidazo[1,2-*a*]pyrazolo[4,3-*e*]pyrimidin-4(6*H*)-one (6d)

White solid, m.p. 151°C to 153°C; IR (KBr) ν_{max} (cm^{-1}): 3201 (NH stretching), 1648 (C═O stretching), 1584 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.92 (s, 3H, CH_3), 3.67 (q, J = 10.8 Hz, 2H, CH_2), 3.80 to 3.87 (m, 2H, CH_2), 4.73 (d, J = 16.8 Hz, 1H, ═CH), 5.02 to 5.06 (m, 2H, CH_2), 5.22 (d, J = 9.6 Hz, 1H, ═CH), 5.98 to 6.07 (m, 1H, ═CH), 7.96 (s, 1H, CH pyrazole); ^{13}C NMR (125 MHz, DMSO-d_6): δ 16.5, 25.9, 54.7, 56.4, 66.5, 104.2, 117.4, 133.4, 137.7, 141.8, 157.2, 163.6; MS: m/z 372 (M + H); Anal. Calcd for $C_{12}H_{14}IN_5O$: C, 38.83; H, 3.80; I, 34.19; N, 18.87; found: C, 38.79; H, 3.77; I, 34.13; N, 18.76.

4.6.5 | 9-(Iodomethyl)-1-(prop-2-enyl)-6,7,8,9-tetrahydropyrazolo[4,3-*e*]pyrimido[1,2-*a*]pyrimidin-4(1*H*)-one (6e)

White solid, m.p. 165°C to 167°C; IR (KBr) ν_{max} (cm^{-1}): 2870 (CH stretching), 1648 (C═O stretching), 1625 (C═N

stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.07 to 2.17 (m, 1H, CH), 2.32 to 2.35 (m, 1H, CH), 3.31 to 3.44 (m, 2H, CH_2), 3.51 to 3.62 (m, 2H, CH_2), 4.72 to 4.77 (m, 1H, CH), 4.90 (d, J = 18.8 Hz, 2H, =CH_2), 5.13 (d, J = 16.4 Hz, 1H, CH), 5.25 (d, J = 11.2 Hz, 1H, CH), 6.06 to 6.14 (m, 1H, =CH), 7.74 (s, 1H, CH pyrazole), 8.64 to 9.02 (m, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 6.0, 22.6, 34.3, 52.8, 54.1, 105.9; 117.1, 134.1, 135.6, 142.6, 151.5, 164.3; MS: m/z 372 (M + H); Anal. Calcd for $C_{12}H_{14}IN_5O$: C, 38.83; H, 3.80; I, 34.19; N, 18.87; found: C, 38.76; H, 3.77; I, 34.16; N, 18.75.

4.7 | General procedure for the synthesis of compounds (8a-e)

A mixture of iodomethyl derivative **6a-e** (2 mmol) and NaN_3 (0.14 g, 2.15 mmol) in DMF (20 mL) was heated at 75°C to 80°C for 1.5 to 2 hours and then cooled. The resulting precipitate was filtered off and washed with diethyl ether (15 mL). After the filtrate was left to stand for 2 to 3 days, an additional amount of the analytically pure product precipitated which was then added to the main portion of the target compound.

4.7.1 | (7aRS,11aSR)-1,2,7a,8,11,11a-hexahydro-4*H*,7*H*-2,2a^1,3,6,6a,9,10,10a-octaazacyclopenta[6,7]cycloocta[1,2,3,4-*jkl*]-as-indacen-4-one (8a)

White solid, m.p. >300°C; IR (KBr) ν_{max} (cm^{-1}): 2802 (CH stretching), 1623 (C=O stretching), 1591 (C=N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.53 to 3.56 (m, 1H, CH), 3.80 to 3.85 (m, 1H, CH), 3.92 to 4.06 (m, 3H, 3CH), 4.19 to 4.42 (m, 3H, 3CH), 4.73 to 4.77 (m, 1H, CH), 5.31 to 5.39 (m, 1H, CH), 7.60 (s, 1H, CH pyrazole), 8.31 to 8.42 (m, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 44.8, 50.2, 50.5, 53.3, 54.5, 69.2, 102.1, 135.4, 142.6, 156.9, 166.0; Anal. Calcd for $C_{11}H_{12}N_8O$: C, 48.53; H, 4.44; N, 41.16; found: C, 48.47; H, 4.39; N, 41.06.

4.7.2 | (7aRS,11aSR)-methyl-1,2,7a,8,11,11a-hexahydro-4*H*,7*H*-2,2a^1,3,6,6a,9,10,10a-octaazacyclopenta[6,7]cycloocta[1,2,3,4-*jkl*]-as-indacen-4-one (8b)

White solid, m.p. 292°C to 294°C; IR (KBr) ν_{max} (cm^{-1}): 1618 (C=O stretching), 1591 (C=N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.96 (s, 3H, CH_3), 3.63 to 3.66 (m, 1H, CH), 3.83 to 3.87 (m, 1H, CH), 3.97 to 4.10 (m, 3H, 3CH), 4.19 to 4.23 (m, 1H, CH), 4.27 to 4.33 (m, 1H, CH), 4.39 to 4.45 (m, 1H, CH), 4.75 to 4.80 (m, 1H, CH), 5.32 to 5.38 (m, 1H, CH), 7.59 (s, 1H, CH pyrazole); ^{13}C NMR (125 MHz, DMSO-d_6 + D_2O): δ 31.6, 50.5, 51.2, 51.9, 52.3, 54.8, 69.0, 101.7, 136.1, 143.3, 155.8, 168.2; Anal. Calcd for $C_{12}H_{14}N_8O$: C, 50.34; H, 4.93; N, 39.14; found: C, 50.26; H, 4.90; N, 39.12.

4.7.3 | (7aRS,11aSR)-2-allyl-1,2,7a,8,11,11a-hexahydro-4*H*,7*H*-2,2a^1,3,6,6a,9,10,10a-octaazacyclopenta[6,7]cycloocta[1,2,3,4-*jkl*]-as-indacen-4-one (8c)

White solid, m.p. >300°C; IR (KBr) ν_{max} (cm^{-1}): 1620 (C=O stretching), 1588 (C=N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.56 to 3.59 (m, 1H, CH), 3.81 to 3.86 (m, 1H, CH), 3.98 to 4.09 (m, 5H, 5CH), 4.22 (d, J = 15.6 Hz, 1H, =CH), 4.27 to 4.41 (m, 2H, 2CH), 4.77 (d, J = 16.0 Hz, 1H, =CH), 5.24 to 5.31 (m, 2H, 2 =CH), 5.34 to 5.41 (m, 1H, CH), 5.82 to 5.91 (m, 1H, =CH), 7.61 (s, 1H, CH pyrazole); ^{13}C NMR (125 MHz, DMSO-d_6): δ 46.7, 49.5, 50.7, 51.0, 52.2, 54.9, 69.7, 102.4, 118.7, 132.6, 136.0, 143.2, 155.2, 166.8; Anal. Calcd for $C_{14}H_{16}N_8O$: C, 53.84; H, 5.16; N, 35.88; found: C, 53.77; H, 5.11; N, 35.83.

4.7.4 | (7aRS,11aSR)-11a-methyl-1,2,7a,8,11,11a-hexahydro-4*H*,7*H*-2,2a^1,3,6,6a,9,10,10a-octaazacyclopenta[6,7]cycloocta[1,2,3,4-*jkl*]-as-indacen-4-one (8d)

White solid, m.p. >300°C (DMF); IR (KBr) ν_{max} (cm^{-1}): 3450 (NH stretching), 1649 (C=O stretching), 1604 (C=N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.63 (s, 3H, CH_3), 3.63 to 3.66 (m, 1H, CH), 3.70 to 3.76 (m, 1H, CH), 3.80 to 3.82 (m, 1H, CH), 3.99 to 4.04 (m, 1H, CH), 4.14 (d, J = 16.0 Hz, 1H, CH), 4.24 to 4.32 (m, 1H, CH), 4.39 to 4.43 (m, 1H, CH), 4.56 to 4.64 (m, 2H, 2CH), 7.68 (s, 1H, CH pyrazole), 8.29 to 8.50 (m, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 27.3, 52.2, 53.9, 54.5, 56.3, 65.4, 67.4, 105.0, 136.3, 142.1, 157.7, 166.1; Anal. Calcd for $C_{12}H_{14}N_8O$: C, 50.34; H, 4.93; N, 39.14; found: C, 50.28; H, 4.92; N, 39.13.

4.7.5 | (8aRS,12aSR)-2,3,8a,9,12,12a-hexahydro-8H-3,3a^1,4,7,10,11,11a,13-octaaza-6,7-ethenocyclopenta[5,6]cycloocta[1,2,3-*de*]naphtalen-5(1*H*)-one (8e)

White solid, m.p. >300°C; IR (KBr) ν_{max} (cm^{-1}): 2869 (CH stretching), 1622 (C=O stretching), 1551 (C=N

stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.99 to 2.02 (m, 1H, CH), 2.07 to 2.17 (m, 2H, CH_2), 3.35 to 3.39 (m, 1H, CH), 3.51 to 3.58 (m, 1H, CH), 3.87 to 3.93 (m, 2H, 2CH), 4.00 to 4.05 (m, 1H, CH), 4.20 to 4.31 (m, 2H, 2CH), 4.49 to 4.56 (m, 1H, CH), 5.02 to 5.06 (m, 1H, CH), 5.14 to 5.17 (m, 1H, CH), 7.58 (s, 1H, CH pyrazole), 8.33 to 8.36 (m, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6 + D_2O): δ 20.3, 33.9, 50.8, 51.3, 53.6, 54.6, 68.1, 104.8, 135.3, 144.5, 151.7, 166.5; Anal. Calcd for $C_{12}H_{14}N_8O$: C, 50.34; H, 4.93; N, 39.14; found: C, 50.29; H, 4.90; N, 39.10.

4.8 | X-ray structure determination

4.8.1 | Crystal data for 8a

$C_{11}H_{12}N_8O$, M = 272.29, monoclinic, space group C2/c, a = 12.115(8), b = 11.244(8), c = 18.304(12)Å, β = 106.92 (2)°, V = 2385(3)Å^3, Z = 8, d_c = 1.516, μ 0.108 мм$^{-1}$, F (000) 1136, crystal size ca. 0.06 × 0.08 × 0.26 mm. All crystallographic measurements were performed at 173 K on a Bruker Smart Apex II diffractometer operating in the ω scans mode. The intensity data were collected within the $\theta_{max} \leq 26.61°$ using Mo-K_α radiation (λ = 0.71078 Å). The intensities of 16 153 reflections were collected (2496 unique reflections, R_{merg} = 0.1279). The structure were solved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation for non-hydrogen atoms using the Bruker SHELXTL program package.[32] All CH hydrogen atoms were placed at calculated positions and refined as "riding" model and H atom by the nitrogen atom were found from difference Fourier synthesis and refined isotropically. Convergence for **8a** was obtained at R1 = 0.0557 and wR2 = 0.1026 for 1319 observed reflections with I ≥ 2σ(I); R1 = 0.1320 and wR2 = 0.1284, GOF = 0.987 for 2496 independent reflections, 186 parameters, the largest and minimal peaks in the final difference map 0.32 and −0.30 e/Å^3.

Crystallographic data for the structure in this paper have been deposited at Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1982420. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK, (fax: +44-[0]1223-336 033 or e-mail: deposit@ccdc.cam.ac.uk).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Vaskevych RI, Vaskevych AI, Rusanov EB, Mel'nyk OY, Vovk MV. Synthesis of new-type 1,3,6-triazocine via intramolecular reactions of iodocyclization and [3+2] azido cycloaddition. *J Heterocyclic Chem*. 2020;1–11. https://doi.org/10.1002/jhet.4028