A Flexible Method for the Synthesis of Chromenopyrimidine Fused Animoazole Scaffolds by Copper Catalyzed Intramolecular Hetero Diels–Alder (IMHDA) Reaction

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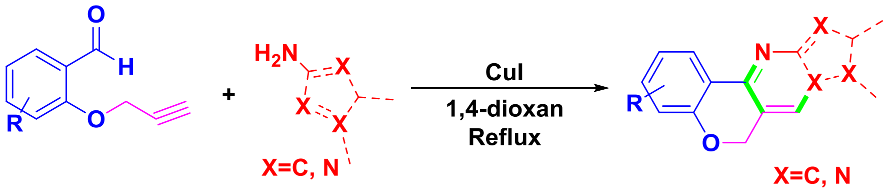


Abstract

A one-pot and efficient copper-catalyzed approach for the synthesis of tetracyclic chromeno pyrimido[1,2-*b*]indazolone derivatives and chromeno[4,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine derivatives as a class of pharmacologically interesting compounds through the intramolecular domino condensation-aza-Diels–Alder reaction of aminoazole compounds and *o*-propargylated salicylaldehydes under reflux conditions has been described.

Keywords: Chromenopyrimidine; animoazole; intramolecular Hetero Diels–Alder (IMHDA) reaction; copper catalyst.

Introduction

Some of the key aspects of green chemistry and ideal synthetic concepts are the use of harmless and inexpensive reagents, and solvents, reduction in the number of steps, and catalysts, in addition to ensuring a high atom economy and minimal waste generation during the reactions[1]. Therefore, it is highly desired to develop simple, highly atomically efficient, and environmentally friendly multiple bond formation reactions such as multi-component and domino reactions[2–4].

One of the best methods for achieving this goal is Diels-Alder reactions. In organic chemistry, the Diels-Alder reaction is a reaction that happens among a conjugated diene with a $4\boldsymbol{\pi}$ electron system and a substituted alkene as a $2\boldsymbol{\pi}$ electron system typically termed the dienophile and affects the formation of a cyclohexane derivative. It is the primary instance of a cyclization reaction with a concerted mechanism. In this approach that the electrons are concurrently transferred in a cyclic style among the diene and the dienophile for the cyclic structure. Therefore, the Diels–Alder reaction happens thru a single, cyclic transition state, without intermediates generated in the course of the route of the reaction. Hence, the Diels–Alder reaction is ruled via way of means orbital symmetry considerations[5,6].

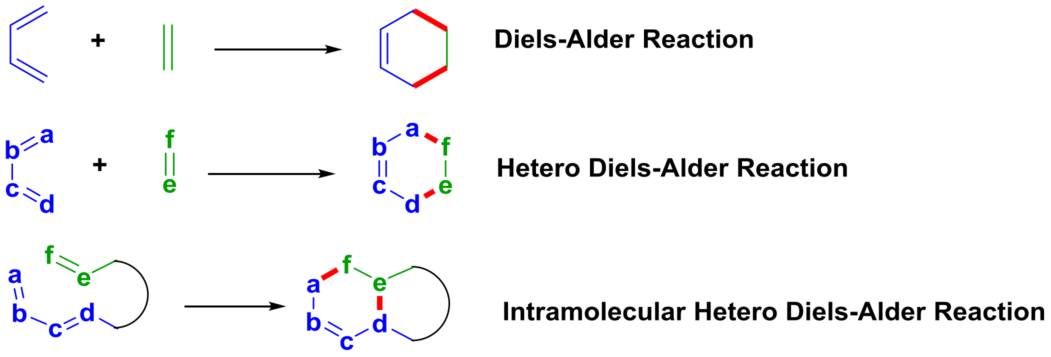
In Diels–Alder reaction, interactions are between the two frontier molecular orbitals (FMO), the highest occupied molecular orbital (HOMO) of a diene with the lowest unoccupied molecular orbital (LUMO) of a dienophile. However, the HOMO–LUMO energy gap is close enough that the roles can be reversed by switching the electronic effects of the substituents on the two components. As a result, this reaction tends to work best with the electron-donating group (EDG) on the diene and the electron-withdrawing group (EWG) on the dienophile[7].

Diels-alder reactions are more specifically classified as thermally allowed [4+2] cycloaddition reactions accordingly to Woodward–Hoffmann rules. Although heat is not required in Diels-Alder reactions, heating up will improve the yield of reaction[8,9].

Due to a concerted mechanism and the simultaneous formation of two new carbon-carbon bonds, the Diels–Alder reaction provides a trustworthy way to form six-membered rings with good control over the regio- and stereochemical products. Consequently, it has provided a powerful and widely practical tool for the preparation of complex molecules in organic chemistry, especially in the synthesis of natural products[10].

Many Diels-Alder reactions have been reported during the last decades but this reaction was first discovered in 1928 by two German chemists, Diels and Alder. This reaction has become one of the most useful reactions in organic chemistry. Due to the importance of this discovery, Diels and Alder won the Nobel Prize in 1950[11].

Undoubtedly, domino Hetero-Diels–Alder (HDA) cycloaddition was one of the most alluring and significant developments in the discovery and establishment of organic compounds[12,13]. Chemists have used the Hetero-Diels–Alder reactions for the preparation of different heterocyclic compounds by exchanging the atoms **a**-**d** in the butadiene as well as the atoms **e** and **f** in the alkene by heteroatoms such as oxygen, nitrogen, sulfur, phosphorous, boron, silicon, and selenium indeed using different heterodienes and heterodienophiles in Diels–Alder reactions[14,15].



Scheme 1. Kinds of Diels–Alder reactions

Among these reactions, the Povarov-type intramolecular reaction ([4 + 2] hetero Diels–Alder reaction) is excellent for constructing polycyclic nitrogen heterocycles due to its economical and sterically controlled properties[16,17]. These reactions allow the simultaneous construction of two or more rings in one step, avoiding continuous chemical transformations and avoiding continuous chemical transformations[18,19].

The main challenge of this approach is the development of a suitable starting material with an aldehyde or amine functional group to which the appropriate dienophile moiety is attached. Most of the known intramolecular Povarov reactions are readily available and are therefore limited to allyl (propargyl) salicylaldehyde derivatives, leading to corresponding benzopyran structures with 6-membered chromen units[20–23]. It is used in the design of frameworks for some natural products with biologically active[24].

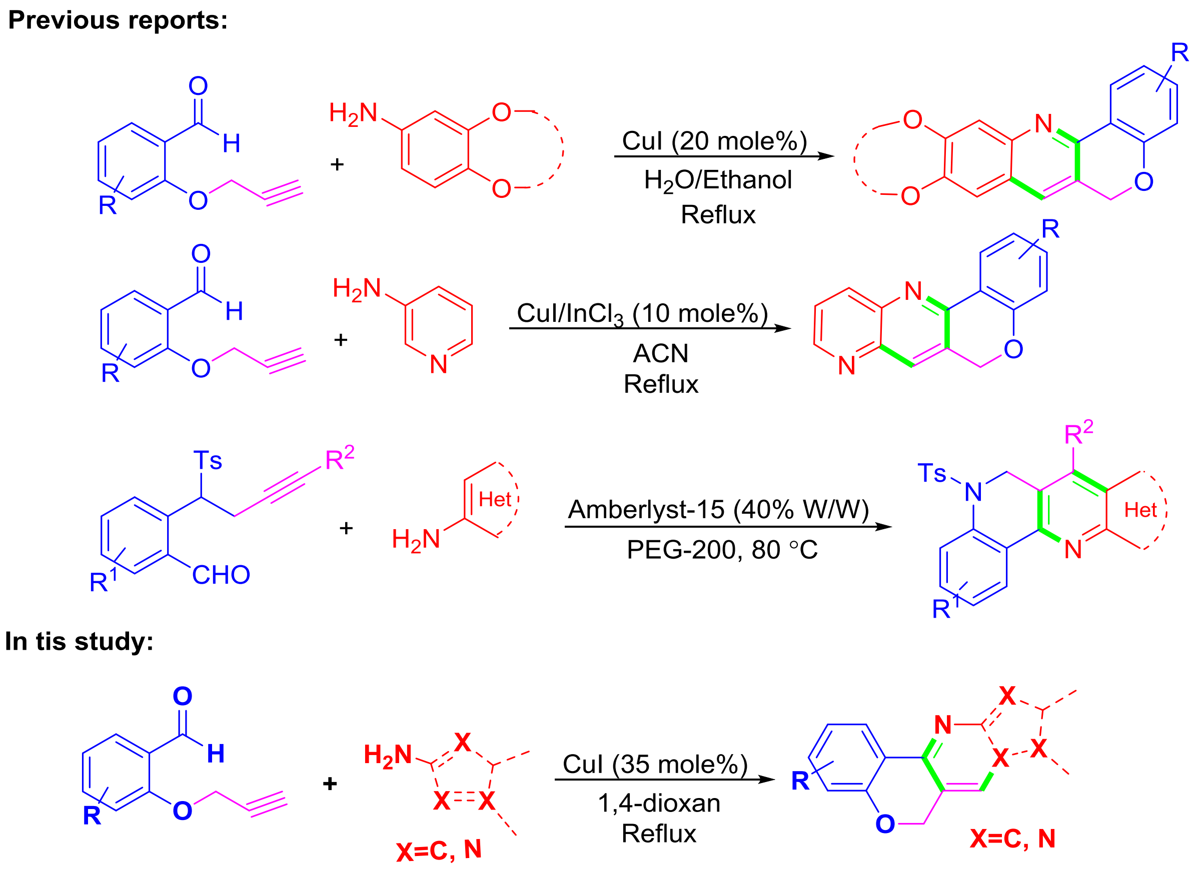
Chromene fused *N*-containing heterocyclic scaffolds are privileged structures due to their remarkable biological and pharmacological activities such as estrogenic, antibacterial, anticancer agents anti-inflammatory activities, serotonin and estrogen receptor functions, and biosensors[25]. Some of these compounds have been used as drugs that modulate the transcriptional activity of the human progesterone receptor, which plays an important role in medicine, and have been used therapeutically[26,27].

This wide range of interesting activities and properties has prompted studies into the development of a convenient and efficient methodology for synthesizing chromene fused *N*-containing heterocyclic scaffolds[28,29].

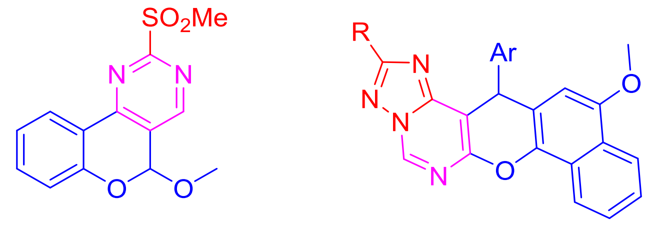
Recently, a few examples involving the use of amine compounds such as amino azole, amino pyridine, simple anilines, etc. were reported in the literature[30,31]. For example in 2018, Maji and Mahalanobish reported a mild and efficient method for the synthesis of chromenonaphthyridine derivatives via domino reaction of aminopyridine and different *o*-propargylated salicylaldehydes using CuI/$InCl_3$ as catalyst[32]. In the same direction, Nagarajan and coworkers reported the synthesis of chromenoquinolines through cyclization of different substituted anilines with *o*-propargylated salicylaldehydes using CuI/$La(OTf)_3$ as catalyst[33]. Sridharan and coworkers reported an efficient protocol for the synthesis of complex hybrid heterocycles containing [1,6]-naphthyridine and coumarin/pyrazole moieties in the presence of the Amberlyst-15 catalyst in PEG-200[34]. In 2018 Mahdavi and coworkers reported a one-pot and efficient copper-catalyzed approach for the synthesis of tetracyclic 6*H*-chromeno[4,3-*b*]quinolones through the intramolecular domino condensation-aza-Diels–Alder reaction of electron-rich anilines and *o*-propargylated salicylaldehydes (Scheme 1)[35]. Indeed, in all reactions 1-aza-1,3-butadienes act as dienes with unactivated alkynes as dienophiles in cyclization Intramolecular Hetero Diels–Alder (IMHDA).

Due to the lower reactivity of inactivated alkynes (unactivated acetylenes) in comparison to the corresponding alkenes various transition metal salts such as copper[36,37], silver[38], gold[39], ruthenium[40] and potentially Lewis acids such as indium trichloride[41,42] and $BF_3{\cdot}OEt_2$[43,44] as catalyst provides new opportunities for construction carbon-carbon or carbon-heteroatom bonds in the present of alkyne. Among them, copper can easily activate the terminal alkyne bond and indium can coordinate with the imine double bond and facilitate in cyclization of Intramolecular Hetero Diels–Alder (IMHDA) due to their commercial availability, stability in the air, inexpensive and non-toxic nature.

In continuation of our research to prepare *N*-containing heterocycles, we report an efficient strategy for the preparation of the tetracyclic compounds through an intramolecular type of hetero-Diels-Alder reaction of 1-aza-1,3-butadienes that was made of aminoazole with unactivated tethered alkynes which results in the formation of chromenopyrimido[1,2-*b*]indazolone derivatives and chromeno[4,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine derivatives as the classes of pharmacological interesting compounds[45–48]. Reactions were carried out in the presence of CuI (35 mole%), and 1,4-dioxane as the solvent. Both scaffolds containing pyrimidine and aminoazole are important classes of nitrogen poly-heterocycles and these structural units are found in numerous pharmaceutically important structures with promising biological activities such as protein kinase inhibitors that can be used to treat cancer cell proliferation, viral infections, Alzheimer’s disease, neurodegenerative disorders, and auto-immune diseases[49–53]. Several marketed drugs constitute the fused-pyrimidine fragment in the main core structure, for instance, divaplon, taniplon, and fasiplon which are used as anxiolytic drugs in many clinics (Scheme 3).



Scheme 2. Amine compounds in Intramolecular Hetero Diels–Alder (IMHDA).



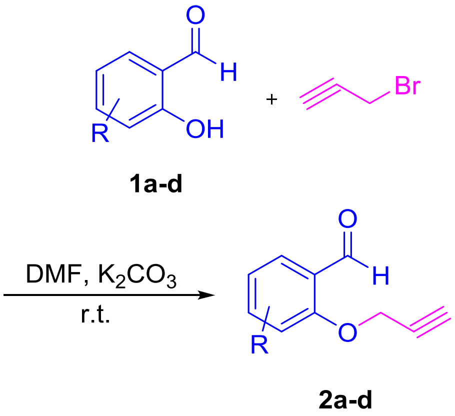
antiplatelet/analgesic

Antimicrobial

Scheme 3. Bioactive compounds containing chromenopyrimide

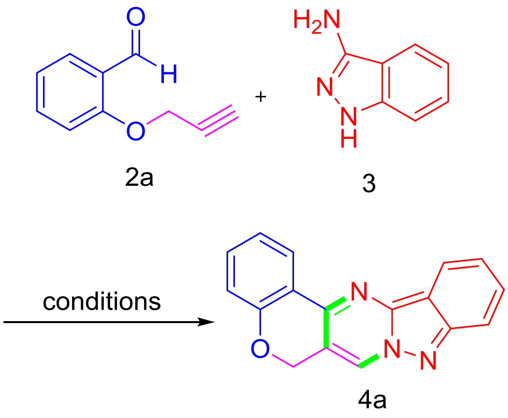
Results and discussion

The *o*-propargylated salicylaldehydes **2a–d** were prepared by the Williamson ether reaction of corresponding substituted salicylaldehydes **1a–d** with propargyl bromide in 88–93% yield (Scheme 3). Cyclization Intramolecular Hetero Diels–Alder (IMHDA) reaction of *o*-propargylated salicylaldehydes (2-(prop-2-yn-1-yloxy)benzaldehyde) **2a,** 1*H*-indazol-3-amine **3**, and CuI as catalyst in ethanol to affording 6*H*-chromeno[4',3':4,5]pyrimido[1,2-*b*]indazole **4a** was investigated as model reaction (Table 1). The reaction was unsuccessful for the intramolecular hetero-Diels–Alder reaction when no catalyst was used in the reaction (Table 1, entry 1). Next, various solvents, different catalysts, various stoichiometric amounts of the catalyst, and the time of reaction were examined. Investigation of solvents indicated that 1,4-dioxane was the best solvent for the reaction among other solvents such as DMSO, DMF, DCE, $CHCl_3$, EtOH, Isopropanol, Toluene, H_2O, DMSO/H_2O, DMF/H_2O, DCE/H_2O and ACN/H_2O (Table 1, entries 2–15). Investigation of other catalysts such as CuBr, CuCl, $CuCl_2$, $CuSO_4$, $BF_3\cdot OEt_2$, and $AuCl_3$ indicated that CuI was to be the best choice for reaction (entries 16-21). Fortunately, increasing the amount of CuI from 10 mole% to 35 mole%, increased the yield remarkably (Table 1, entries 22–24). When the amount of CuI was further increased to 40 mole%, the yield of **4a** almost remained unchanged (entry 25). Increasing in the amount of **3** from 1 equiv. to 1.5 equivs., increased the yield, When the amount of **3** was further increased to 3 equivs., the yield of **4a** almost remained unchanged (entries 26-27). When the time was further increased from 24h to 36h, the yield of **4a** almost remained unchanged (entry 28). Therefore, the optimal condition for the reaction was established based on the screening results and was as follows: **1a** (0.5 mmol, 1 equiv.), **3**(0.75 mmol, 1.5 equiv.), and CuI 35 mole% in 1,4-dioxane reflux condition for 24 hours.



Scheme 4. Synthesis of *o*-propargylated salicylaldehydes

Tale 1. reaction conditions [a]



Entry	Cat	Solvent	Yield (%)[b] 4a
1	—	EtOH	0
2	CuI 10 mole%	DMSO	25
3	CuI 10 mole%	DMF	17
4	CuI 10 mole%	DCE	0
5	CuI 10 mole%	ACN	32
6	CuI 10 mole%	$CHCl_3$	0
7	CuI 10 mole%	EtOH	trace
8	CuI 10 mole%	Toluene	32
9	CuI 10 mole%	H_2O	trace
10	CuI 10 mole%	Isopropanol	trace
11	CuI 10 mole%	1,4-dioxane	48
12	CuI 10 mole%	DMF/H_2O	trace
13	CuI 10 mole%	ACN/H_2O	27
14	CuI 10 mole%	DMSO/H_2O	14
15	CuI 10 mole%	DCE/H_2O	trace
16	CuBr 10 mole%	1,4-dioxane	41
17	CuCl 10 mole%	1,4-dioxane	45
18	$CuSO_4$ 10 mole%	1,4-dioxane	15

19	$CuCl_2$ 10 mole%	1,4-dioxane	18
20	$BF_3 \cdot OEt_2$ (10 mol%)	1,4-dioxane	24
21	$AuCl_3$ 10 mole%	1,4-dioxane	trace
22	CuI 20 mole%	1,4-dioxane	58
23	CuI 30 mole%	1,4-dioxane	66
24	CuI 35 mole%	1,4-dioxane	78
25	CuI 40 mole%	1,4-dioxane	78
26	CuI 50 mole%	1,4-dioxane	77
27	CuI 35 mole%	1,4-dioxane	86c
28	CuI 35 mole%	1,4-dioxane	86d
29	CuI 35 mole%	1,4-dioxane	86e

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[a] Reaction conditions: **2a** (0.5 mmol), 3 (1 equiv.), catalyst (1 equiv.), solvent (1 mL), r.t.,24 h; [b] Isolated yields; [c] **3** (1.5 equivs.); [d] **3** (3 equivs.); [e] 36 h.

To investigate the scope of this reaction, the reaction between *o*-propargylated salicylaldehydes derivatives **2a–d** and 1H-indazol-3-amine 3were explored under optimized conditions resulting in high yields with efficiencies of 80 to 90% (**4a-d**), as shown in Table 2.

The products were separated by column chromatography and the structures were assigned based on spectroscopic studies. The ^{1}H NMR spectrum of compound **4a** exhibited one singlet at δ 5.48 ppm for enantiotopic methylene protons (CH_2), and a singlet at δ 9.39 ppm for protons of the pyrimidine ring (CH), four doublets, and four triplets for benzene rings.

Having optimized the reaction conditions for the synthesis of 6*H*-chromeno[4,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine derivatives (**6a-d**), we conducted the cyclization Intramolecular Hetero Diels–Alder (IMHDA) reaction by employing 4*H*-1,2,4-triazol-3-amine **5** with aldehydes **2a–c,** the results are summarized in Table 3.

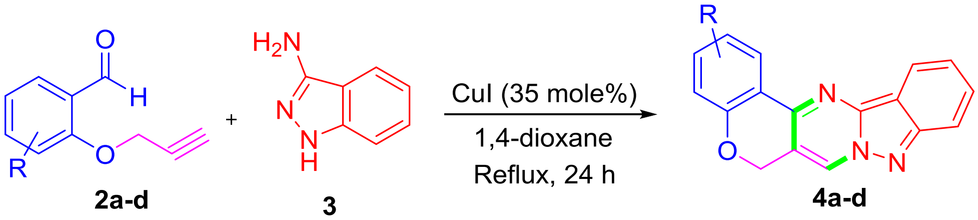
The products were separated by column chromatography and the structures were assigned based on spectroscopic studies. The ^{1}H NMR spectrum of compound **6a** exhibited one singlet at δ 5.38 ppm for enantiotopic methylene protons (CH_2), a singlet at δ 9.35 ppm for protons of the pyrimidine ring (CH), a singlet at δ 8.63 ppm for protons of the Triazole ring (CH).

A plausible mechanism for the copper-catalyzed intramolecular domino condensation and aza-Diels–Alder formation is proposed in Scheme 4. Initially, imine **A** (1-aza-1,3-butadienes) is formed from the condensation between *o*-propargylated salicylaldehyde and related amnioazole compounds. It is reasonable to assume that the copper-acetylide imine intermediate **B** was formed by deprotonation in the presence of the copper catalyst and the formation of a π-complex with CuI[54]. Research has shown that copper(I) salts can be coordinated to the triple bond and act as a π-electrophilic Lewis acid. Next, the sequential intramolecular [4+2] cycloaddition and oxidation generate the desired product (Scheme 3).

Conclusion

In summary, an efficient approach was developed for the synthesis of chromeno pyrimido[1,2-*b*]indazolone derivatives and chromeno[4,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine derivatives as the class of pharmacologically interesting compounds via the copper-catalyzed intramolecular domino condensation and aza-Diels–Alder reaction of aminoazole **3** and **5** with *o*-propargylated salicylaldehydes.

Table 2. Scope of Intramolecular Hetero Diels–Alder (IMHDA) for compound **3**



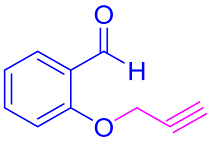
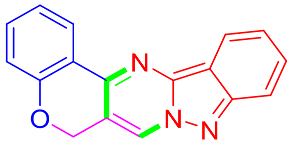
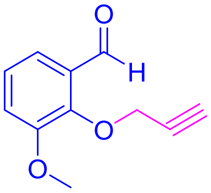
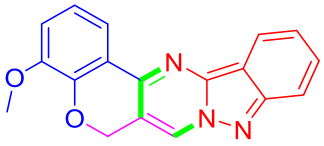
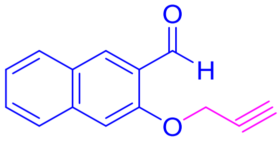
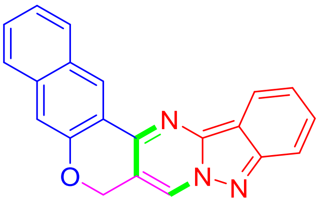
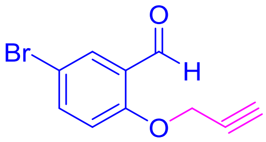
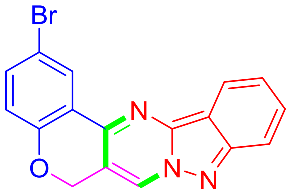
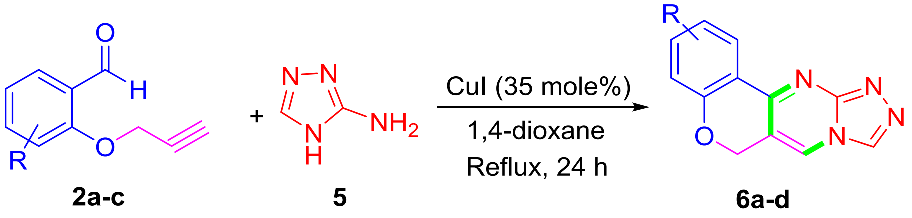
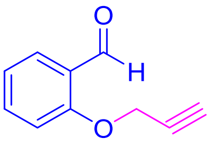
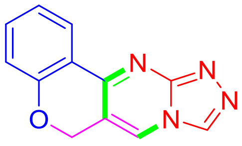
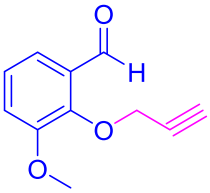
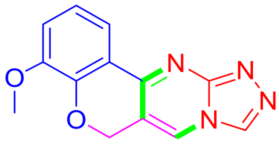
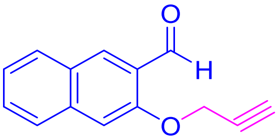
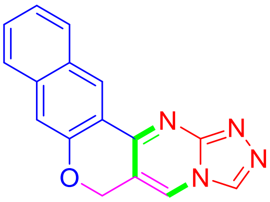
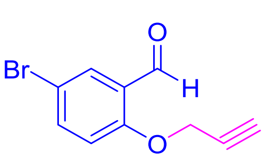
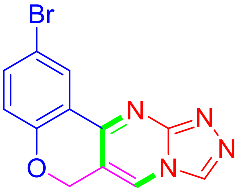
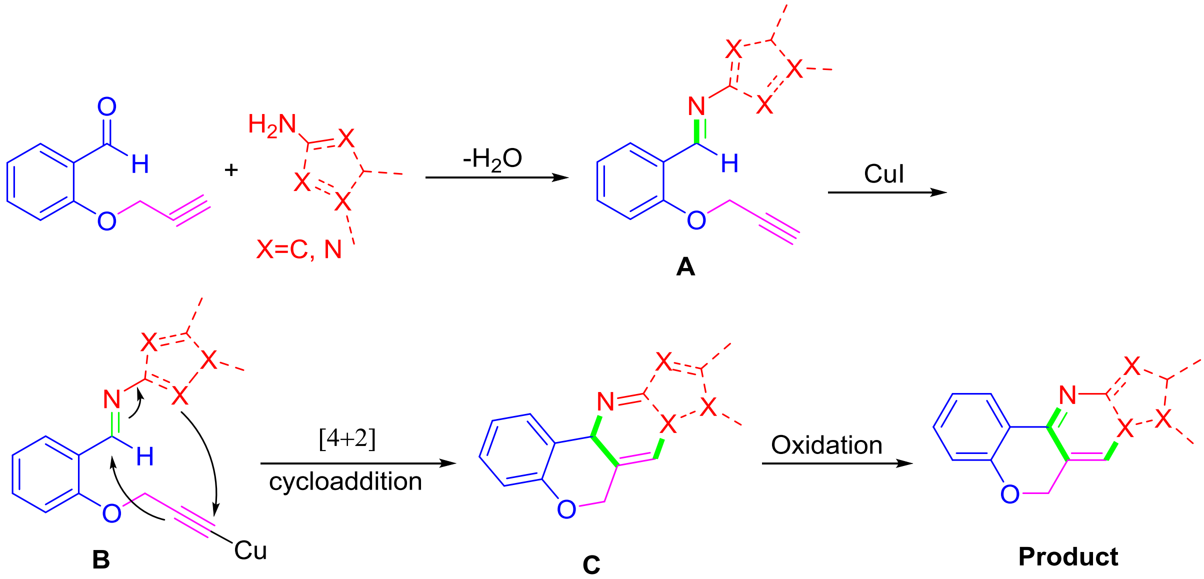
Entry	**2a-d**	**4a-d**	Yield
1		 **4a**	80
2		 **4b**	90
3		 **4c**	85
4		 **4d**	80

Table 3. Scope of Intramolecular Hetero Diels–Alder (IMHDA) for compound **5**



Entry	**2a-d**	**6a-d**	Yield
1		 **6a**	88

2		 **6b**	91
3		 **6c**	83
4		 **6d**	78



Scheme 5. A plausible mechanism

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker (bruker avance III 400) (400 and 100 MHz, respectively) and Bruker (Bruker Avance FT- 500) (500 and 125 MHz, respectively) NMR spectrometers in DMSO-d_6 using tetramethylsilane (TMS) as internal standard. Mass spectra (ESI) were recorded on an HP (Agilent technologies) 5937 Mass Selective Detector. Elemental analyses were performed using a CHN-Rapid Heraeus elemental analyzer (Wellesley, MA). Melting points were determined in a capillary tube and are not corrected. The progress of the reaction was followed with TLC using silica gel SILG/UV 254 and 365 plates.

All chemicals were purchased from Merck and Fluka companies.

Synthesis of pyrimido[1,2-*b*]indazoles 4a–d (General method), A mixture of 2-propargyl salicylaldehyde **2a–d** (0.5 mmol), 1*H*-indazol-3-amine **3** (0.75 mmol), CuI (35 mol %), in 1,4-dioxane (5 ml) was stirred in a sealed vessel for 24 h under reflux. After completion of the reaction, the reaction mixture was cooled to room temperature, solvent evaporated and solid residue purified by column chromatography on silica gel, eluent *n*-hexane/ethyl acetale (90:10, v/v).

6*H*-Chromeno[4',3':4,5]pyrimido[1,2-*b*]indazole (4a). Yield 105.1 mg (77%), yellow solid, mp 189–191°C. ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 9.39 (1H, s, H-7); 8.40–8.32 (1H, m, H-1); 8.28 (1H, d, *J* = 8.3, H-10); 7.80 (1H, d, *J* = 8.7, H-13); 7.68–7.58 (1H, m, H-11); 7.49 (1H, d, *J* = 7.9, H-3); 7.31 (1H, t, *J* = 7.5, H-2); 7.24 (1H, t, *J* = 7.5, H-12); 7.14–7.06 (1H, m, H-4); 5.48 (2H, s, 6-CH$_2$). ^{13}C NMR spectrum (125 MHz), δ, ppm: 150.8; 147.0; 144.4; 143.1; 133.3; 130.6; 129.9; 127.2; 125.5; 122.7; 122.1; 121.1; 118.1; 116.5; 116.1; 114.2; 65.2. Mass spectrum, *m/z*: 273 [M+H]$^+$. Found, %: C 74.66; H 3.91; N 15.52. $C_{17}H_{11}N_3O$. Calculated, %: C 74.71; H 4.06; N 15.38.

4-Methoxy-6*H*-chromeno[4',3':4,5]pyrimido[1,2-*b*]indazole (4b). Yield 119.7 mg (79%), yellow solid, mp 181–183°C. ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 9.39 (s, 1H), 8.29 (d, *J* = 8.1 Hz, 1H), 7.93 (dd, *J* = 7.3, 2.1 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.23 – 7.15 (m, 2H), 5.47 (s, 2H), 3.86 (s, 3H). ^{13}C NMR spectrum (125 MHz), δ, ppm: 151.3; 149.3; 147.1; 145.5; 143.3; 133.2; 130.1; 122.8; 122.4; 121.1; 121.1; 117.3; 116.7; 116.5; 115.6; 113.2; 65.8; 56.3. Mass spectrum, *m/z*: 303.18 [M+H]$^+$. Found: C, 71.53; H, 4.18; N, 13.95. $C_{18}H_{13}N_3O_2$. Calculated, C, 71.28; H, 4.32; N, 13.85.

7*H*-Benzo[6',7']chromeno[4',3':4,5]pyrimido[1,2-*b*]indazole (4c). Yield 137.3 mg (85%), yellow solid, mp 222–224°C. ^{1}H NMR spectrum (400 MHz) δ, ppm (*J*, Hz): 9.23 (d, *J* = 2.6 Hz, 1H), 8.15 (d, *J* = 2.1 Hz, 1H), 7.85 (dd, *J* = 8.9, 3.4 Hz, 1H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.63 (d, *J* = 9.1 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.45 (d, *J* = 6.9 Hz, 1H), 7.39 (dd, *J* = 9.1, 2.1 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.10 (dd, *J* = 8.9, 2.3 Hz, 2H), 5.24 (d, *J* = 1.4 Hz, 2H). ^{13}C NMR spectrum (100 MHz) δ, ppm:151.3; 147.0; 144.9; 142.1; 134.7; 132.1; 130.7; 130.7; 129.1; 128.8; 126.8; 125.3; 121.1; 121.1; 120.0; 118.7; 118.5; 117.0; 116.6; 114.4; 65.8. Mass spectrum, *m/z*: 323.17 [M+H]$^+$. Found: C, 78.16; H, 4.14; N, 12.91. $C_{21}H_{13}N_3O$. Calculated, C, 78.00; H, 4.05; N, 13.00.

2-Bromo-6*H*-chromeno[4',3':4,5]pyrimido[1,2-*b*]indazole (4d). Yield 140.4 mg (80%), yellow solid, mp 205–207°C. ^{1}H NMR spectrum (400 MHz) δ, ppm (*J*, Hz): 9.42 (d, *J* = 1.2 Hz, 1H), 8.42 (d, *J* = 2.5 Hz, 1H), 8.35 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 8.6 Hz, 1H), 7.67 – 7.63 (m, 2H), 7.33 (dd, *J* = 8.2, 6.8 Hz, 1H), 7.11 (d, *J* = 8.7 Hz, 1H), 5.52 (d, *J* = 1.2 Hz, 2H). ^{13}C NMR spectrum (125 MHz) δ, ppm: 151.7; 146.3; 143.9; 142.5; 134.9; 133.7; 130.6; 128.1; 126.7; 124.3; 122.3; 121.3; 118.9; 117.2; 115.9; 114.6;, 66.2. Mass spectrum, *m/z*: 351.06 [M+H]$^+$. Found: C, 58.14; H, 2.72; N, 12.13. $C_{17}H_{10}BrN_3O$. Calculated, C, 57.98; H, 2.86; N, 11.93.

Synthesis of [1,2,4]triazolo[4,3-*a*]pyrimidines 6a–d (General method). A mixture of 2-propargyl salicylaldehyde (0.5 mmol), 4*H*-1,2,4-triazol-3-amine **5** (0.75 mmol), CuI (35 mol %), in 1,4-dioxane (5 ml) was stirred in a sealed vessel for 24 h under reflux. After completion of the reaction, the reaction mixture was cooled to room temperature, solvent evaporated and solid residue was purified by column chromatography on silica gel, eluent *n*-hexane/ethyl acetale (90:10, v/v)..

6*H*-Chromeno[4,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine (6a). Yield 88.5 mg (79%), yellow solid, mp 214–216°C. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 9.36 (s, 1H), 8.64 (s, 1H), 8.25 (d, *J*=7.90 Hz, 1H), 7.55 (d, *J*=7.70 Hz, 1H, H_{Ar}), 7.23 (t, *J*=7.40 Hz ,1H), 7.11 (d, *J*=8.20 Hz), 5.38 (s, 2H). ^{13}C NMR spectrum (100 MHz), δ, ppm: 158.2; 156.6; 155.3; 153.8; 134.7; 133.1; 126.1; 121.1; 118.2; 115.6; 65.4. Mass spectrum, *m/z*: 224.14 $[M+H]^+$. Found: C, 64.44; H, 3.72; N, 25.15. $C_{12}H_8N_4O$. Calculated, C, 64.28; H, 3.60; N, 24.99.

4-Methoxy-6*H*-chromeno[4,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine (6b). Yield 96.5 mg (76%), yellow solid, mp 195–197°C. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 9.36 (s, 1H), 8.64 (s, 1H), 7.82 (d, *J*=7.80 Hz, 1H), 7.25 (d, *J*=7.50 Hz, 1H), 7.16 (t, J=8.00 Hz ,1H), 5.37 (s, 2H), 3.85 (s, 3H). ^{13}C NMR spectrum (100 MHz), δ, ppm: 156.6; 155.3; 154.0; 149.3; 147.9; 133.0; 122.9; 121.8; 117.2; 116.6; 115.6; 65.4; 56.3. Mass spectrum, *m/z*: 254.13 $[M+H]^+$. Found: C, 61.69; H, 3.74; N, 22.31. $C_{13}H_{10}N_4O_2$. Calculated, C, 61.41; H, 3.96; N, 22.04.

6*H*-Benzo[6,7]chromeno[4,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine (6c). Yield 100.0 mg (73%), yellow solid, mp 231–232°C. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 9.62 (d, *J*=8.70 Hz, 1H), 9.40 (s, 1H), 8.67 (s, 1H), 8.13 (d, *J*=8.80 Hz, 1H), 7.99 (d, *J*=8.10 Hz, 1H), 7.73 (t, *J*=7.80 Hz ,1H), 7.44(t, *J*=7.50 Hz, 1H), 7.32 (d, *J*=8.80 Hz, 1H), 5.37 (s, 2H),. ^{13}C NMR spectrum (100 MHz), δ, ppm: 159.4; 156.6; 155.1; 154.9; 136.0; 132.5; 130.7; 130.7; 130.5; 129.3; 128.9; 126.7; 125.4; 118.9; 116.6; 113.9; 65.6. Mass spectrum, *m/z*: 274.17 $[M+H]^+$. Found: C, 70.28; H, 3.83; N, 22.23. $C_{13}H_{10}N_4O_2$. Calculated, C, 70.06; H, 3.68; N, 20.43.

2-Bromo-6*H*-chromeno[4,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine (6d). Yield 117.8 mg (78%), yellow solid, mp 212–214°C. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 9.35 (s, 1H), 8.67 (s, 1H), 7.48 (d, *J* = 2.1 Hz, 1H), 7.29 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 5.35 (s, 2H).^{13}C NMR spectrum (100 MHz), δ, ppm: 158.3; 156.1; 155.1; 152.9; 135.0; 133.2; 131.8; 129.8; 121.6; 117.5; 114.1; 65.1.

Mass spectrum, *m/z*: 302.04 $[M+H]^+$. Found: C, 47.32; H, 2.57; N, 18.24. Calculated, $C_{12}H_7BrN_4O$. Calculated, C, 47.55; H, 2.33; N, 18.48;.

Supplementary information file containing ^{1}H and ^{13}C NMR spectra of all synthesized compounds is available at the journal website http://hgs.osi.lv.

References

1. Wender, P. A.; Miller, B. L. *Nature* **2009**, *460*, 197.
2. Gholami, F.; Moazzam, A.; Hosseini, S.; Larijani, B.; Adib, M.; Mahdavi, M. *Tetrahedron Lett*. **2022**, *100*, 153859.
3. Rahmati, A.; Moazzam, A.; Khalesi, Z. *Tetrahedron Lett.* **2014**, *55*, 3840.
4. Moazzam, A.; Jafarpour, F. *New J. Chem.* **2020**, *44*, 16692.
5. Jorgensen, K. A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3558.
6. Eschenbrenner-Lux, V.; Kumar, K.; Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **2014**, *53*, 11146.
7. Gallier, F. *Curr. Org. Chem*. **2022**, *20*, 2222.
8. Holmes, H. L. *Organic Reactions*; *John Wile*y & Sons, Inc.: *Hoboken, NJ, USA,* **2011**, 60.
9. Wessig, P.; Müller, G. *Chem. Rev*. **2008**, *108*, 2051.
10. Sara, A. A.; Um-e-Farwa, U-e-F.; Saeed, A.; Kalesse, M. Synthesis **2022**, 54, 975.
11. Diels, O.; Alder KJ. *Justus Liebigs Ann. Chem*. 1928, 460, 98-122 .
12. Tietze, L. F.; Kettschau, G. *Hetero Diels-Alder Reactions in Organic Chemistry.* **2008**, *189*, 1.
13. Goulaouic-dubois, C.; Adams, D. R.; Sisti, N. J.; Fowler, F. W.; Grierson, D. S.; Chimie, D.; Naturelles, S. *Tetrahedron Lett*. **1998**, *39*, 4283.
14. Xu, G.; Bai, X.; Dang, Q. *Acc. Chem. Res.* **2020**, *53*, 773.
15. Borah, H. N.; Deb, M. L.; Boruah, R. C.; Bhuyan, P. J. *Tetrahedron Lett.* **2005**, *46*, 3391.
16. Fochi, M.; Caruana, L.; Bernardi, L. *Synthesis* **2013**, *46*, 135.

17. S. Bello Forero, J.; Jones Junior, J.; M. da Silva, F. *Curr. Org. Chem.* **2015**, *13*, 157.

18. Adolfsson, D. E.; Tyagi, M.; Singh, P.; Deuschmann, A.; Ådén, J.; Gharibyan, A. L.; Jayaweera, S. W.; Lindgren, A. E. G.; Olofsson, A.; Almqvist, F. *J. Org. Chem.* **2020**, *85*, 14174.

19. Kand, D.; Kalle, A. M.; Varma, S. J.; Talukdar, P. *Chem. Commun*. **2012**, *48*, 2722.

20. Khoshkholgh, M. J.; Balalaie, S.; Gleiter, R.; Rominger, F. *Tetrahedron* **2008**, *64*, 10924.

21. Jayagobi, M.; Raghunathan, R. *Tetrahedron Asymmetry* **2010**, *21*, 2726.

22. Arepalli, S. K.; Lee, C.; Sim, S.; Lee, K.; Jo, H.; Jun, K. Y.; Kwon, Y.; Kang, J. S.; Jung, J. K.; Lee, H. *Bioorg. Med. Chem.* **2018**, *26*, 5181.

23. Arepalli, S. K.; Park, B.; Jung, J. K.; Lee, K.; Lee, H. *Tetrahedron Lett.* **2017**, *58*, 449.

24. Heravi, M. M.; Ahmadi, T.; Ghavidel, M.; Heidari, B.; Hamidi, H. *RSC Adv.* **2015**, *5*, 101999.

25. Shaikh, M. H.; Subhedar, D. D.; Khedkar, V. M.; Jha, P. C.; Kalam, F. A.; Sangshetti, J. N.; Shingate, B. B. And Molecular Docking Study. **2016**, *27*, 1058.

26. Wang, Z. X.; Lia, B.; Xing, Z.; Chen, L. Z.; Han, G. F. *J. Chem. Res.* **2014**, *38*, 480.

27. Okasha, R. M.; Albalawi, F. F.; Afifi, T. H.; Fouda, A. M.; Al-Dies, A. A. M.; El-Agrody, A. M. *Molecules* **2016**, *21*, 1.

28. Jadhav, A. M.; Balwe, S. G.; Jeong, Y. T. *Tetrahedron Lett.* **2019**, *60*, 151251.

29. Akrami, S.; Karami, B.; Farahi, M. *J. Heterocycl. Chem.* **2020**, *57*, 2446.

30. Singal, K. K.; Singh, B.; Raj, B. *Synth. Commun.* **1993**, *23*, 107.

31. Laschat, S.; Lauterwein, J. *J. Org. Chem.* **1993**, *58*, 2856.

32. Maji, P. K.; Mahalanobish, A. *Heterocycles* **2018**, *96*, 42.

33. Ramesh, S.; Gaddam, V.; Nagarajan, R. *Synlett* **2010**, *3*, 757.

34. Muthukrishnan, I.; Vachan, B. S.; Karuppasamy, M.; Eniyaval, A.; Uma Maheswari, C.; Nagarajan, S.; Menéndez, J. C.; Sridharan, V. *Org. Biomol. Chem.* **2019**, *17*, 6872.

35. Rahimzadeh, G.; Soheilizad, M.; Kianmehr, E.; Larijani, B.; Mahdavic, M. *Arkivoc* **2018**, *2018*, 20.

36. Bieber, L. W.; da Silva, M. F. *Tetrahedron Lett.* **2004**, *45*, 8281.

37. Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810.

38. Wei, C.; Li, Z.; Li, C.-J. *Org. Lett.***2003**, *5*, 4473.

39. Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584.

40. Bruneau, C.; Neveux, M.; Kabouche, Z.; Ruppin, C.; Dixneuf, P. H. *Synlett* **1991**, *1991*, 755.

41. Gupta, R.; Jain, A.; Madan, Y. *J. Heterocycl. Chem.* **2013**, *50*, 1342.

42. Zhang, J.; Li, C.-J. *J. Org. Chem.* **2002**, *67*, 3969.

43. Palacios, F.; Alonso, C.; Arrieta, A.; Cossío, F. P.; Ezpeleta, J. M.; Fuertes, M.; Rubiales, G. *Eur. J. Org. Chem.* **2010**, *2010*, 2091.

44. Alonso, C.; González, M.; Palacios, F.; Rubiales, G. *J. Org. Chem.* **2017**, *82*, 6379.

45. Abdel, A.; El, M. S.; Abdelhamid, A. O. *Eur. J. Chem.* **2012**, *3*, 455.

46. Zonouzi, A.; Hosseinzadeh, F.; Karimi, N.; Mirzazadeh, R.; Ng, S. W. *ACS Comb. Sci.* **2013**, *15*, 240.

47. Murlykina, M. V.; Morozova, A. D.; Zviagin, I. M.; Sakhno, Y. I.; Desenko, S. M.; Chebanov, V. A. *Front. Chem.* **2018**, *6*, 1–43.

48. Yakaiah, T.; Kurumurthy, C.; Lingaiah, B. P. V; Narsaiah, B.; Pamanji, R.; Velatooru, L. R.; Rao, J. V.; Gururaj, S.; Parthasarathy, T.; Sridhar, B. *Med. Chem. Res.* **2012**, 21, 4261.

49. Prachayasittikul, S.; Pingaew, R.; Worachartcheewan, A.; Sinthupoom, N.; Prachayasittikul, V.; Ruchirawat, S.; Prachayasittikul, V. *Mini-Rev. Med. Chem.* **2017**, *17*, 869.

50. Baluja, S.; Hirapara, A.; Lava, D. J. *anal. pharm. res.* **2018**, *7*, 540.

51. Al-Masoudi, N. A.; Al-Salihi, N. J.; Marich, Y. A.; Markus, T. *J. Fluoresc.* **2015**, *25*, 1847.

52. Cherukupalli, S.; Karpoormath, R.; Chandrasekaran, B.; Hampannavar, G. A.; Thapliyal, N.; Palakollu, V. N. *Eur. J. Med. Chem.* **2017**, *126*, 298.

53. Singh, U. P.; Bhat, H. R.; Verma, A.; Kumawat, M. K.; Kaur, R.; Gupta, S. K.; Singh, R. K. *RSC Adv.* **2013**, *3*, 17335.

54. Sheykhi, S.; Pedrood, K.; Amanlou, M.; Larijani, B.; Mahdavi, M., *Tetrahedron*, **2021**, *102*, 132524.