chemistry proceedings

MDPI

Proceeding Paper

Reaction of Some Substituted (Un)Substituted Isatins with 1,ω-Alkanes and Their Products with Sodium Azide †

Nguyen Minh Tri [1,2], Vu Ngoc Toan [1,2], Hoang Mai Linh [1], Ngo Thi Ngoc Mai [1], Tran Thi-Hai-Yen [1], Ngo Thi Thuy [1], Nguyen Thi Thuy Huong [1], Pham Thi Thuy Van [1], Tran Thi Hai Yen [1], Nguyen Thi Kim Giang [3], Hoang Thi Kim Van [4] and Nguyen Dinh Thanh [1,*]

1 Faculty of Chemistry, VNU University of Science (Vietnam National University, Ha Noi), 19 Le Thanh Tong, Hoan Kiem, Ha Noi 100000, Vietnam; nguyenminhtri.hkt@gmail.com (N.M.T.); vngoctoanvktqs@gmail.com (V.N.T.); hoangmailinh_t62@hus.edu.vn (H.M.L.); ngothingocmai_t62@hus.edu.vn (N.T.N.M.); tranthihaiyen1_t62@hus.edu.vn (T.T.-H.-Y.); thuyngond24091999@gmail.com (N.T.T.); huongho13101999@gmail.com (N.T.T.H.); thuyvan05011999@gmail.com (P.T.T.V.); haitranyen99@gmail.com (T.T.H.Y.)

2 Institute of New Technology, Academy of Military Science and Technology, Ministry of Defence, 17 Hoang Sam, Cau Giay, Ha Noi 100000, Vietnam

3 Institute of Science and Technology, Ministry of Public Security of Vietnam, 47 Pham Van Dong, Cau Giay, Ha Noi 100000, Vietnam; giang20783@gmail.com

4 Faculty of Chemical Technology, Viet Tri University of Industry, Tien Kien, Lam Thao, Phu Tho 290000, Vietnam; hoangthikimvanviettri@gmail.com

* Correspondence: nguyendinhthanh@hus.edu.vn; Tel.: +84-04-3826-1853; Fax: +84-04-3824-1140

† Presented at the 25th International Electronic Conference on Synthetic Organic Chemistry, 15–30 November 2021; Available online: https://ecsoc-25.sciforum.net/.

Abstract: Azide derivatives of isatins were the initial materials needed for click chemistry, so as to form 1,2,3-triazoles in order to synthesize the hybrid compounds of 1,2,3-triazole–isatin with monosaccharide moieties. The required substituted isatins were prepared according to the Sandmeyer method from corresponding substituted anilines. *N*-(ω-bromoalkyl) isatins were prepared through the nucleophilic reaction, S_N2, of (un)substituted isatins with appropriate dibromoalkanes. Some ω-azidoalkylisatins were synthesized by the reaction of corresponding ω-bromoalkylisatins with sodium azide. The reactions were performed in dry DMF as solvents in the presence of K_2CO_3 as the base and KI as the promoting agent. The product yields reached 30–85%.

Keywords: azide; alkylation; azidation dibromoalkanes; isatins

Citation: Tri, N.M.; Toan, V.N.; Linh, H.M.; Mai, N.T.N.; Thi-Hai-Yen, T.; Thuy, N.T.; Huong, N.T.T.; Van, P.T.T.; Yen, T.T.H.; Giang, N.T.K.; et al. Reaction of Some Substituted (Un)Substituted Isatins with 1,ω-Alkanes and Their Products with Sodium Azide. *Chem. Proc.* **2022**, *8*, 11. https://doi.org/10.3390/ecsoc-25-11716

Academic Editor: Julio A. Seijas

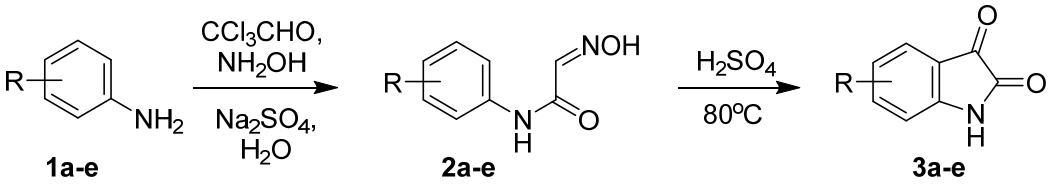
Published: 14 November 2021

1. Introduction

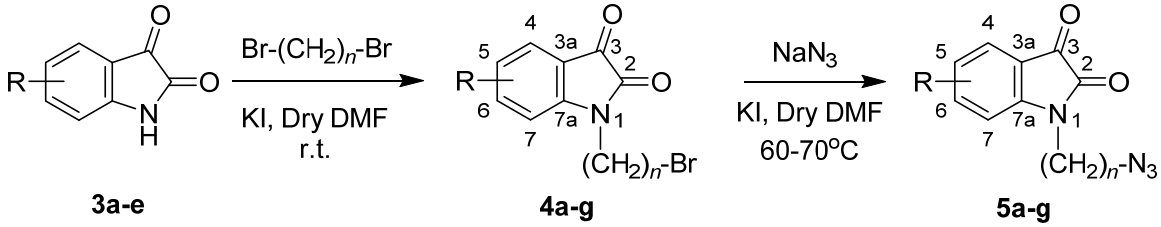
The chemistry of isatin is of interest to chemists [1] because the derivatives of isatin, such as hydrazones [2] and thiosemicarbazones [3], and hybrid compounds containing simultaneous isatin rings and other heterocycles, have diverse biological activities [4–6], including antiviral, antibacterial, anticancer, anticonvulsant, and antidepressant activity [7–9]. Isatin and its derivatives showed specific reactivity towards electrophiles [6,10], including alkyl halides (*N*-alkylation), formaldehyde and amines (Mannich reaction), halogens (halogenation on the aromatic nucleus), acyl chlorides or anhydrides (*N*-acylation), and sulfonyl chlorides (*N*-sulfonylation). Among the reactions of isatin, the substitution of the reactions of hydrogen atoms with N–H bonds on position N-1 was shown to be particularly important [6,10]. An alkylation reaction was used in order to functionalize isatin and its derivatives and was carried out by reactions with alkyl halide in the presence of bases (such as sodium or calcium hydrides, potassium or cesium carbonates) [11]. A variety of methods have been developed for the *N*-alkylation of isatins to target products with high yields, such as iodin and *tert*-butyl hydroperoxide in DMSO as solvent (to produce isatin *N*-methyl and *N*-benzyl isatins) [12], 2-iodoxybenzoic acid-SO_3K in DMSO–water at

60 °C (to produce isatin *N*-methyl and *N*-benzyl isatins) [13], and oxygen and *tert*-butyl nitrite in THF (to produce isatin, *N*-methyl, *N*-phenyl, *N*-benzyl, and *N*-Boc isatins) [14]. However, these methods cannot be used for the synthesis of isatins with the *N*-propargyl group because 1-alkyne can be changed under these reaction conditions. By using this method, direct *N*-alkylation was performed easily and produced high yields of *N*-alkyl isatins [11,15,16]. Some of the more general methods include the use of sodium hydride for substrate activation in nucleophilic substitution reactions in DMF at 25–80 °C [17], as well as the use of the following bases: calcium hydride in DMF at 40–60 °C for 2–4 h with yields of 21–96% [18,19], or at 100 °C for 4 h, with a yield of 89% [20]; anhydrous K_2CO_3 or Cs_2CO_3 in DMF (r.t. at 80 °C for 5–24 h) in the presence of KI, with yields of 25–93% [21]; K_2CO_3/DMF (with yields of 76–94%) or NaOEt/EtOH (with yields of 24–81%) in a domestic microwave oven [15]; and K_2CO_3 or Cs_2CO_3, DMF or *N*-methyl-2-pyrrolidinone (NMP) [11], and K_2CO_3/KI in acetonitrile under microwave conditions (160 °C, 10 min) [22], and in DMF at 150 °C for 5–15 min under microwave irradiation, with product yields of 53–96% [23].

Among *N*-alkyl isatins, *N*-(ω-azidoalkyl) isatins play an important role in the conversion of isatin rings into isatin/1,2,3–triazole hybrid compounds [24–27]. Isatin derivatives with azido groups or 1-alkyne components (*N*-propargylated isatins) are one of two reagents necessary for click chemistry [28–31]. The synthesis of *N*-functionalized isatins with a ω-azidoalkyl group made these derivatives the azido components in click chemistry. Therefore, in this article, we report on the synthesis of some (un)substituted 2-amino-7-hydroxy-4H-chromene-3- carbonitriles via a one-pot, three-component reaction in aqueous media (Schemes 1 and 2).



Scheme 1. Synthetic route for substituted isatins from corresponding anilines, where, **1a–e**,**2a–e**,**3a–e:** R = 5-Me, *n* = 4 (**a**); 7-Me, *n* = 4 (**b**); 5-Et, *n* = 4 (**c**); 5-*i*Pr, *n* = 4 (**d**); 5-F, *n* = 3 (**e**).



Scheme 2. Synthetic route for substituted *N*-(ω-azidoalkyl) isatins from corresponding isatins, where, **3a–e**,**4a–e**,**5a–e:** R = 5-Me, *n* = 4 (**a**); 7-Me, *n* = 4 (**b**); 5-Et, *n* = 4 (**c**); 5-*i*Pr, *n* = 4 (**d**); 5-F, *n* = 3 (**e**); H, *n* = 3 (**f**); H, *n* = 4 (**g**).

2. Results and Discussion

With the exception of isatin that could not be made available for use (for the preparation of ω-bromoalkyl compounds **4f–g** and ω-azidoalkyl compounds **5f–g**, respectively), the remaining isatins (**3a–g**) were synthesized from anilines corresponding to **1a–g**, containing appropriate substituents, by the Sandmeyer reaction of the *N*-isonitrosoacetanilide derivatives **2a–g** (Scheme 1). The **2a–e** compounds were easily obtained through the reaction of these anilines with chloral hydrate and hydroxylamine in a solution of saturated sodium sulfate [32,33]. The *N*-(ω-bromoalkyl) isatin derivatives were synthesized through the nucleophile reaction of the corresponding 1,ω-dibromoalkane derivatives to the appropriate isatins (Scheme 2). This alkylization reaction was carried out in the dry DMF solvent

in the presence of anhydrous potassium carbonate as a base. Potassium iodide was added in order to promote this nucleophilic substituted reaction. The reaction was carried out by stirring the reaction mixture at temperatures of 25–27 °C.

Next, the ω-bromoalkylisatins **4a–g** were converted into ω-azidoalkyl derivatives through a reaction with sodium azide. The potassium iodide was also used as a promoter for this reaction. The reaction was carried out by heating on a water-bath at 70 °C. The reaction times were 1.5–3 h. The end of the reaction was determined by TLC with the solvent system of *n*-hexane/ethyl acetate at a ratio of 7:3 (in volume). The results are represented in Table 1.

Table 1. Synthesis of ω-azidoalkyl derivatives **5a–g.**

Compound	R	*n*	Reaction Time (h)	Yield (%)
5a	5-Me	4	1.5	79
5b	7-Me	4	1.5	46
5c	5-Et	4	2	70
5d	5-iPr	4	2	85
5e	5-F	3	1.5	62
5f	H	3	1,5	35
5g	H	4	3	76

The formation of azide derivatives from the corresponding bromo derivatives of the aforementioned isatins was identified by the IR spectra. Figure 1 displays the IR spectra comparison of representative compounds, including *N*-(4-bromoprop) isatin and the corresponding azide derivative, *N*-(4-azidopropyl) isatin. This showed that the stretching vibrations of the two functional groups, C=O of lactam and C=O ketone, were virtually unchanged, whereas a strong absorption band appeared at ν = 2092 cm^{-1} in the IR spectrum of the azide derivative. This confirmed that the conversion of the bromide derivatives into the azide derivatives was successful. The ketone carbonyl group of **5a–g** compounds was characteristically absorbed in the region at ν = 1738–1726 cm^{-1}. The characteristic band of the >C=O lactam group was located in the ν = 1622–1620 cm^{-1} region; in some cases, this absorption band was superimposed by the stronger absorption band of the ketone carbonyl group.

The ^{1}H NMR spectra of the **5a–g** compounds showed the resonance signals of all the protons in the molecule, including signals in the δ = 7.66–7.04 ppm region for the aromatic protons (Figure 2). The methylene protons in the alkane chains attached to the nitrogen atoms of the isatin appeared in the region at δ= with δ = 4.05–3.67 ppm for the methylene groups associated with the nitrogen–isatin. The methylene group associated with the azido group had signals located at the upfield, at δ = 3.39–3.36 ppm. The methylene groups in the middle of the alkane chains had chemical shifts in the higher fields (δ = 1.69–1.18 ppm). The alkyl groups attached to the benzene aromatic rings had distinct resonance signals; for example, the 5-methyl group had δ = 2.27 ppm, and the 7-methyl group had δ = 2.48 ppm.

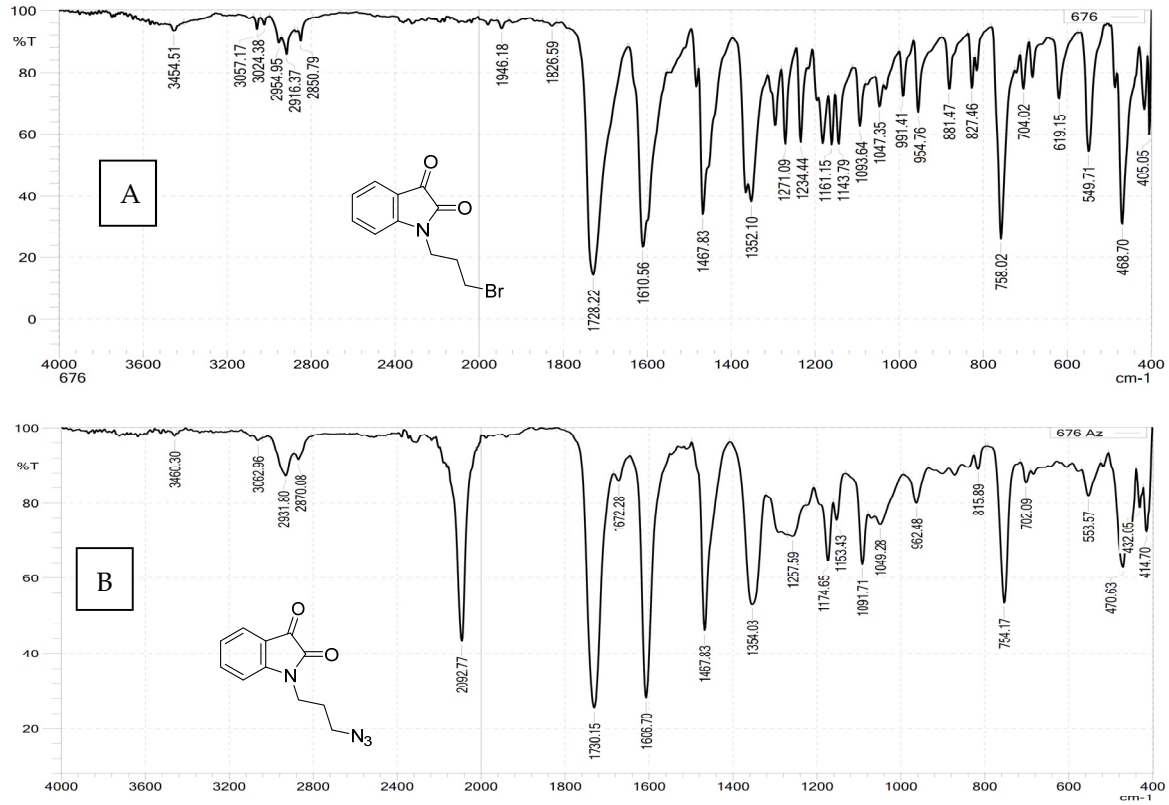


Figure 1. Comparisons of IR spectra of *N*-(3-bromopropyl) isatin **4g** (**A**) and *N*-(3-azidopropyl) isatin **5g** (**B**).

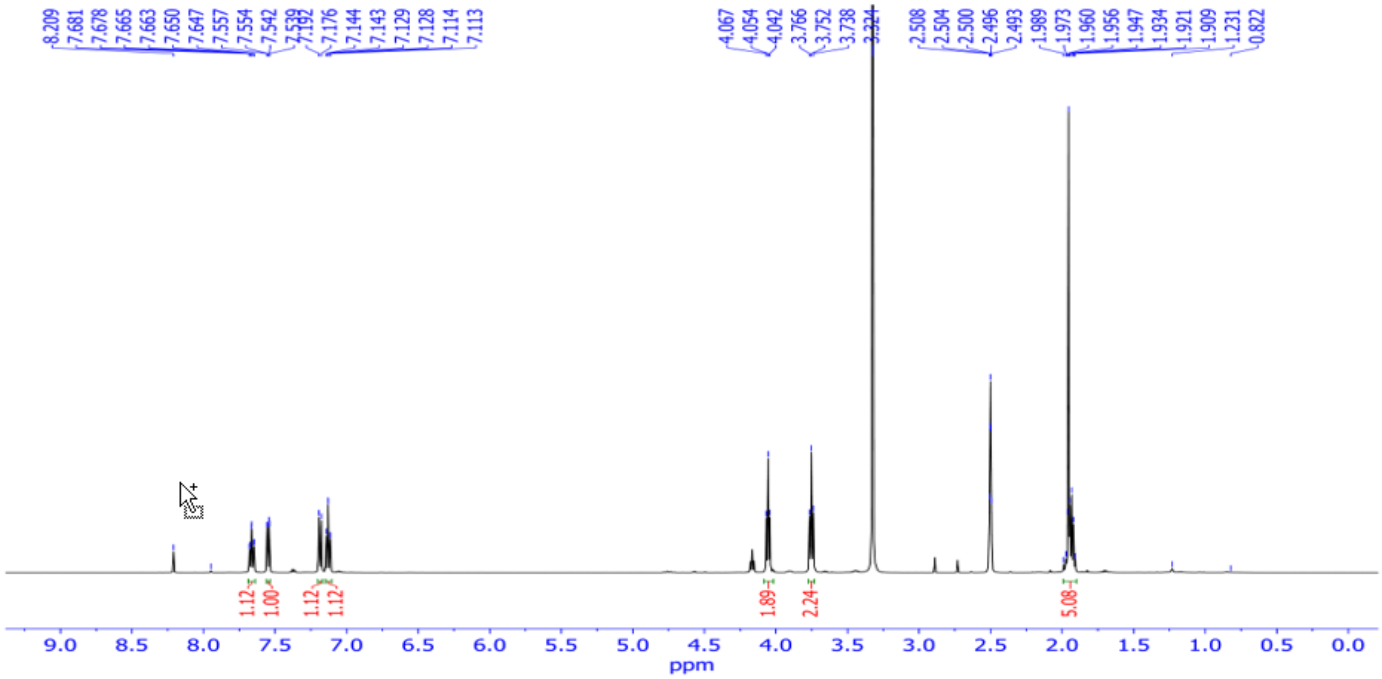


Figure 2. ^{1}H NMR spectra of *N*-(3-azidopropyl) isatin **5g**.

3. Conclusions

N-(ω-bromoalkyl) isatins were synthesized from appropriate isatins and converted into corresponding *N*-(ω-azidoalkyl) isatin derivatives with yields of 35–85%. The structures of the azide derivatives were confirmed by IR spectrum and 1H NMR.

4. Experimental Procedure

The melting points were determined by the open capillary method on STUART SMP3 (BIBBY STERILIN, UK). The IR spectra were recorded by FT-IR Affinity-1S Spectrometer (Shimadzu, Japan) in KBr pellet. The ^{1}H NMR spectra were recorded at 500 MHz (on an Avance AV500 Spectrometer, Bruker, Bremene, Germany) and at 600 MHz (on an AvanceNEO Spectrometer, Bruker, Germany), and ^{13}C NMR spectra at 125 and 160 MHz, respectively, using DMSO-d_6 as solvent and TMS as an internal standard. ESI-mass spectra were recorded on LC-MS LTQ Orbitrap XL (Thermo Fisher Scientific Inc., USA) in methanol/dichloromethane or methanol using ESI method. The analytical thin-layer chromatography (TLC) was performed on silica gel 60WF_{254} No. 5715 aluminum sheets (Merck, Germany) with toluene:ethyl acetate (1:1 by volume) as solvent system, and spots were visualized directly due to the colors of the corresponding isatin derivatives. All chemical reagents were high in purity (reagent grade for organic synthesis) and purchased from the Merck Chemical Company.

General Procedure for Synthesis of N-(ω-azidoalkyl) Isatins (**5a**–**g**)

A reaction mixture consisting of *N*-(ω-bromoalkyl) isatins (**4a**–**g**, 1 mmol), sodium azide (1.5 mmol, 945 mg), and some KI crystals in anhydrous DMF (5 mL) was stirred in a water-bath at a temperature of 70–75 °C for 1.5–3 h. The reaction was monitored by thin-layer chromatography. After the reaction finished, water (10 ml) was added to the mixture to quench the reaction and to dissolve the inorganic salts. The mixture was extracted with ethyl acetate (3×5 mL). The combined extract was dried with anhydrous sodium sulfate. The drying agent was filtered out. After distilling the solvent, the product was isolated from the residue by column chromatography on silica gel with the appropriate solvent system.

N-(4-azidobutyl)-5-methylisatin (**5a**): From **4a** (1 mmol, 296 mg). Yield: 204 mg. M.p. 48–50 °C. IR (KBr), ν (cm^{-1}): 2928, 2867, 2098, 1737, 1622, 1599, 1491, 1346, and 822; ^{1}H NMR (DMSO-d_6), δ (ppm): 7.45 (d, *J* = 2.0, 8.0 Hz, 1H, H-6), 7.34 (d, *J* = 2.0 Hz, 1H, H-4), 7.08 (d, *J* = 8.0 Hz, 1H, H-7), 3.66 (t, *J* = 6.75 Hz, 2H, >N**CH_2**$CH_2CH_2CH_2N_3$), 3.36 (t, *J* = 6.5 Hz, 2H, >$NCH_2CH_2CH_2$**CH_2**N_3), 2.27 (s, 3H, 5-**CH_3**), 1.68–1.63 (m, 2H, >NCH_2**CH_2**$CH_2CH_2N_3$), and 1.61–1.56 (m, 2H, >NCH_2CH_2**CH_2**CH_2N_3).

N-(4-azidobutyl)-7-methylisatin (**5b**): From **4b** (1 mmol, 296 mg). Yield: 119 mg. IR (KBr), ν (cm^{-1}): 3024, 2939, 2870, 2092, 1726, 1597, 1485, 1346, 1305, and 781; ^{1}H NMR (DMSO-d_6), δ (ppm): 7.46 (d, *J* = 7.0 Hz, 1H, H-4), 7.40 (dd, *J* = 1.5, 7.0 Hz, 1H, H-6), 7.04 (t, *J* = 7.0 Hz, 1H, H-5), 3.85 (t, *J* = 7.0 Hz, 2H, >N**CH_2**$CH_2CH_2CH_2N_3$), 3.39 (t, *J* = 7.75 Hz, 2H, >$NCH_2CH_2CH_2$**CH_2**N_3), 2.48 (s, 3H, 7-**CH_3**), 1.69–1.66 (m, 2H, >NCH_2**CH_2**$CH_2CH_2N_3$), and 1.65–1.59 (m, 2H, >NCH_2CH_2 **CH_2**CH_2N_3).

N-(4-azidobutyl)-5-ethylisatin (**5c**): From **4c** (1 mmol, 310 mg). Yield: 190 mg. IR (KBr), ν (cm^{-1}): 2964, 2931, 2870, 2090, 1728, 1618, 1487, 1346, 1168, and 827; ^{1}H NMR (DMSO-d_6), δ (ppm): 7.51 (dd, *J* = 1.5, 8.0 Hz, 1H, H-6), 7.38 (d, *J* = 1.5 Hz, 1H, H-4), 7.11 (d, *J* = 8.0 Hz, 1H, H-7), 3.67 (t, *J* = 7.5 Hz, 2H, >N**CH_2**$CH_2CH_2CH_2N_3$), 3.36 (t, *J* = 6.75 Hz, 2H, >$NCH_2CH_2CH_2C$**H_2**N_3), 2.58 (q, *J* = 7.5 Hz, 2H, 5-**CH_2**CH_3), 1.69–1.63 (m, 2H, >NCH_2**CH_2**$CH_2CH_2N_3$), 1.62–1.56 (m, 2H, >NCH_2CH_2**CH_2**CH_2N_3), and 1.16 (t, *J* = 7.5 Hz, 3H, 5-CH_2**CH_3**).

N-(4-azidobutyl)-5-isopropylisatin (**5d**): From **5d** (1 mmol, 324 mg). Yield: 243 mg. IR (KBr), ν (cm^{-1}): 2958, 2868, 2092, 1732, 1620, 1597, 1487, 1352, and 1174; ^{1}H NMR (DMSO-d_6), δ (ppm): 7.55 (dd, *J* = 2.0, 8.0 Hz, 1H, H-6), 7.42 (d, *J* = 2.0 Hz, 1H, H-4), 7.12 (d, *J* = 8.0 Hz, 1H, H-7), 3.67 (t, *J* = 6.75 Hz, 2H, >N**CH_2**$CH_2CH_2CH_2N_3$), 3.36 (t, *J* = 6.75 Hz, 2H, >$NCH_2CH_2CH_2$**CH_2**N_3), 2.90 [quintet, *J* = 7.0 Hz, 1H, 5-**CH(**$CH_3)_2$], 1.69–1.63 (m, 2H, >NCH_2**CH_2**$CH_2CH_2N_3$), 1.61–1.56 (m, 2H, >NCH_2CH_2**CH_2**CH_2N_3), and 1.19 [d, *J* = 7.0 Hz, 6H, 5-CH**$CH_3)_2$**].

N-(3-azidopropyl)-5-fluoroisatin (**5e**): From **5e** (1 mmol, 286 mg). Yield: 154 mg. IR (KBr), ν (cm^{-1}): 3069, 2933, 2873, 2094, 1730, 1620, 1608, 1481, 1261, 1168, and 823; ^{1}H NMR (DMSO-d_6), δ (ppm): 7.5 (td, J_{FH} = 2.75 Hz, J_{HH} = 9.0 Hz, 1H, H-6), 7.45 (dd, J_{HH} = 2.5 Hz, J_{FH} = 7.0 Hz, 1H, H-4), 7.22 (dd, J_{FH} = 3.75 Hz, J_{HH} = 9.0 Hz, 1H, H-7), 3.73 (t, *J* = 6.75 Hz, 2H, >N**CH$_2$**CH$_2$CH$_2$N$_3$), 3.44 (t, *J* = 6.75 Hz, 2H, >NCH$_2$CH$_2$**CH$_2$**N$_3$), and 1.84 (quintet, *J* = 6.75 Hz, 2H, >NCH$_2$**CH$_2$**CH$_2$N$_3$).

N-(3-azidopropyl) Isatin (**5f**): From **5f** (1 mmol, 268 mg). Yield: 81 mg (35%). IR (KBr), ν (cm^{-1}): 3062, 2931, 2870, 2092, 1730, 1606, 1467, 1354, 1091, and 754; ^{1}H NMR (DMSO-d_6), δ (ppm): 7.66 (td, *J* = 1.5, 8.0 Hz, 1H, H-6), 7.55 (dd, *J* = 0.5, 7.5 Hz, 1H, H-4), 7.18 (d, *J* = 8.0 Hz, 1H, H-7), 7.13 (td, *J* = 0.5, 7.5 Hz, 1H, H-5), 4.05 (t, *J* = 6.25 Hz, 2H, >N**CH$_2$**CH$_2$CH$_2$N$_3$), 3.75 (t, *J* = 6.25 Hz, 2H, >NCH$_2$CH$_2$**CH$_2$**N$_3$), and 1.93 (quintet, *J* = 6.25 Hz, 2H, >NCH$_2$**CH$_2$**CH$_2$N$_3$).

N-(4-azidobutyl) Isatin (**5g**): From **5g** (1 mmol, 282 mg). Yield: 185 mg. IR (KBr), ν (cm^{-1}): 3062, 2935, 2874, 2069, 1738, 1611, 1468, 1360, 1092, and 753; ^{1}H NMR (DMSO-d_6), δ (ppm): 7.65 (td, *J* = 1.0, 8.0 Hz, 1H, H-6), 7.53 (d, *J* = 7.5 Hz, 1H, H-4), 7.19 (d, *J* = 8.0 Hz, 1H, H-7), 7.12 (t, *J* = 7.5 Hz, 1H, H-5), 3.69 (t, *J* = 7.0 Hz, 2H, >N**CH$_2$**CH$_2$CH$_2$CH$_2$N$_3$), 3.56 (t, *J* = 6.75 Hz, 2H, >NCH$_2$CH$_2$CH$_2$**CH$_2$**N$_3$), 1.88 (quintet, *J* = 7.0 Hz, 2H, >NCH$_2$**CH$_2$**CH$_2$CH$_2$N$_3$), and 1.74 (sextet, *J* = 7.0 Hz, 2H, >NCH$_2$CH$_2$**CH$_2$**CH$_2$N$_3$).

Author Contributions: Conceptualization, N.D.T. and N.M.T.; methodology, N.D.T. and N.M.T.; investigation, data curation, writing (original draft preparation), all authors; review and editing, visualization, supervision, project administration, funding acquisition, N.D.T. and N.M.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Vietnam National Foundation for Science and Technology Development (NAFOSTED) under grant number 104.01-2020.01.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Singh, G.S.; Desta, Z.Y. Isatins As Privileged Molecules in Design and Synthesis of Spiro-Fused Cyclic Frameworks. *Chem. Rev.* **2012**, *112*, 6104–6155. [CrossRef] [PubMed]
2. Rabia, M.K.; Mohamad, A.D.M.; Ismail, N.M.; Mahmoud, A.A. Synthesis, characterization, anti-fungi and anti-bacterial activity of new [(2-pyridyl)-3-isatin]-bishydrazone. *Russ. J. Gen. Chem.* **2013**, *83*, 2406–2412. [CrossRef]
3. Muğlu, H.; Çavuş, M.S.; Bakır, T.; Yakan, H. Synthesis, characterization, quantum chemical calculations and antioxidant activity of new bis-isatin carbohydrazone and thiocarbohydrazone derivatives. *J. Mol. Struct.* **2019**, *1196*, 819–827. [CrossRef]
4. Abdel-Aziz, H.A.; Eldehna, W.M.; Keeton, A.B.; Piazza, G.A.; Kadi, A.A.; Attwa, M.W.; Abdelhameed, A.S.; Attia, M.I. Isatin-benzoazine molecular hybrids as potential antiproliferative agents: Synthesis and in vitro pharmacological profiling. *Drug Des. Dev. Ther.* **2017**, *11*, 2333–2346. [CrossRef] [PubMed]
5. Al-Wabli, R.I.; Zakaria, A.S.; Attia, M.I. Synthesis, Spectroscopic Characterization and Antimicrobial Potential of Certain New Isatin-Indole Molecular Hybrids. *Molecules* **2017**, *22*, 1958. [CrossRef]
6. Varun; Sonam; Kakkar, R. Isatin and its derivatives: A survey of recent syntheses, reactions, and applications. *MedChemComm* **2019**, *10*, 351–368. [CrossRef]
7. Pakravan, P.; Kashanian, S.; Khodaei, M.M.; Harding, F.J. Biochemical and pharmacological characterization of isatin and its derivatives: From structure to activity. *Pharmacol. Rep.* **2013**, *65*, 313–335. [CrossRef]
8. Gabr, M.T.; El-Gohary, N.S.; El-Bendary, E.R.; El-Kerdawy, M.M.; Ni, N. Isatin-β-thiocarbohydrazones: Microwave-assisted synthesis, antitumor activity and structure-activity relationship. *Eur. J. Med. Chem.* **2017**, *128*, 36–44. [CrossRef]
9. Guo, H. Isatin derivatives and their anti-bacterial activities. *Eur. J. Med. Chem.* **2019**, *164*, 678–688. [CrossRef]
10. Silva, J.F.M.d.; Garden, S.J.; Pinto, A.C. The chemistry of isatins: A review from 1975 to 1999. *J. Braz. Chem. Soc.* **2001**, *12*, 273–324. [CrossRef]
11. Shmidt, M.S.; Reverdito, A.M.; Kremenchuzky, L.; Perillo, I.A.; Blanco, M.M. Simple and Efficient Microwave Assisted *N*-Alkylation of Isatin. *Molecules* **2008**, *13*, 831–840. [CrossRef] [PubMed]

12. Zi, Y.; Cai, Z.-J.; Wang, S.-Y.; Ji, S.-J. Synthesis of Isatins by I_2/TBHP Mediated Oxidation of Indoles. *Org. Lett.* **2014**, *16*, 3094–3097. [CrossRef] [PubMed]
13. Bredenkamp, A.; Mohr, F.; Kirsch, S.F. Synthesis of Isatins through Direct Oxidation of Indoles with IBX-SO_3K/NaI. *Synthesis* **2015**, *47*, 1937–1943. [CrossRef]
14. Ying, W.-W.; Zhu, W.-M.; Liang, H.; Wei, W.-T. Synthesis of Indoline-2,3-diones by Radical Coupling of Indolin-2-ones with *tert*-Butyl Hydroperoxide. *Synlett* **2018**, *29*, 215–218. [CrossRef]
15. Azizian, J.; Fallah-Bagher-Shaidaei, H.; Kefayati, H. A facile one-pot method for the preparation of *N*-alkyl isatins under microwave irradiation. *Synth. Commun.* **2003**, *33*, 789–793. [CrossRef]
16. Thanh, N.D.; Giang, N.T.K.; Quyen, T.H.; Huong, D.T.; Toan, V.N. Synthesis and evaluation of in vivo antioxidant, in vitro antibacterial, MRSA and antifungal activity of novel substituted isatin *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazones. *Eur. J. Med. Chem.* **2016**, *123*, 532–543. [CrossRef]
17. Tacconi, G.; Righetti, P.P.; Desimoni, G. Einfache Darstellung *N*-substituierten Isatinen. *J. Prakt. Chem.* **1973**, *315*, 339–344. [CrossRef]
18. Garden, S.J.; Torres, J.C.; da Silva, L.E.; Pinto, A.C. A Convenient Methodology for *N*-Alkylation of Isatin Compounds. *Synth. Commun.* **1998**, *28*, 1679–1689. [CrossRef]
19. Vadivel, V.; Ganesan, R.; Kannaiyan, V.; Vellikannu, E.; Vijayakumar, T. Synthesis of Substituted Isatins from the MBH Adduct of 1,5,6-Trisubstituted Isatins Using (2,4-Dinitrophenyl)hydrazine and K-10 Clay Explored as Protection–Deprotection Chemistry. *ACS Omega* **2019**, *4*, 9563–9568. [CrossRef]
20. Lötter, A.N.C.; Pathak, R.; Sello, T.S.; Fernandes, M.A.; van Otterlo, W.A.L.; de Koning, C.B. Synthesis of the dibenzopyrrocoline alkaloid skeleton: Indolo[2,1-a]isoquinolines and related analogues. *Tetrahedron* **2007**, *63*, 2263–2274. [CrossRef]
21. Vine, K.L.; Locke, J.M.; Ranson, M.; Pyne, S.G.; Bremner, J.B. An Investigation into the Cytotoxicity and Mode of Action of Some Novel N-Alkyl-Substituted Isatins. *J. Med. Chem.* **2007**, *50*, 5109–5117. [CrossRef] [PubMed]
22. Bridges, T.M.; Marlo, J.E.; Niswender, C.M.; Jones, C.K.; Jadhav, S.B.; Gentry, P.R.; Plumley, H.C.; Weaver, C.D.; Conn, P.J.; Lindsley, C.W. Discovery of the First Highly M5-Preferring Muscarinic Acetylcholine Receptor Ligand, an M5 Positive Allosteric Modulator Derived from a Series of 5-Trifluoromethoxy N-Benzyl Isatins. *J. Med. Chem.* **2009**, *52*, 3445–3448. [CrossRef] [PubMed]
23. Wee, X.K.; Yeo, W.K.; Zhang, B.; Tan, V.B.C.; Lim, K.M.; Tay, T.E.; Go, M.-L. Synthesis and evaluation of functionalized isoindigos as antiproliferative agents. *Bioorg. Med. Chem.* **2009**, *17*, 7562–7571. [CrossRef] [PubMed]
24. Singh, P.; Sharma, P.; Anand, A.; Bedi, P.M.S.; Kaur, T.; Saxena, A.K.; Kumar, V. Azide-alkyne cycloaddition en route to novel 1*H*-1,2,3-triazole tethered isatin conjugates with in vitro cytotoxic evaluation. *Eur. J. Med. Chem.* **2012**, *55*, 455–461. [CrossRef]
25. Jin, X.; Xu, Y.; Yang, X.; Chen, X.; Wu, M.; Guan, J.; Feng, L. Design, synthesis and in vitro anti-microbial evaluation of ethylene/propylene-1*H*-1, 2, 3-triazole-4-methylene-tethered isatin-coumarin hybrids. *Curr. Top. Med. Chem.* **2017**, *17*, 3213–3218. [CrossRef]
26. Shaikh, M.H.; Subhedar, D.D.; Khan, F.A.K.; Sangshetti, J.N.; Nawale, L.; Arkile, M.; Sarkar, D.; Shingate, B.B. Synthesis of Novel Triazole-incorporated Isatin Derivatives as Antifungal, Antitubercular, and Antioxidant Agents and Molecular Docking Study. *J. Heterocycl. Chem.* **2017**, *54*, 413–421. [CrossRef]
27. Singh, H.; Singh, J.V.; Gupta, M.K.; Saxena, A.K.; Sharma, S.; Nepali, K.; Bedi, P.M.S. Triazole tethered isatin-coumarin based molecular hybrids as novel antitubulin agents: Design, synthesis, biological investigation and docking studies. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 3974–3979. [CrossRef]
28. MacDonald, J.P.; Badillo, J.J.; Arevalo, G.E.; Silva-García, A.; Franz, A.K. Catalytic Stereoselective Synthesis of Diverse Oxindoles and Spirooxindoles from Isatins. *ACS Comb. Sci.* **2012**, *14*, 285–293. [CrossRef]
29. Nisha; Kumar, K.; Bhargava, G.; Land, K.M.; Chang, K.-H.; Arora, R.; Sen, S.; Kumar, V. N-Propargylated isatin-Mannich mono- and bis-adducts: Synthesis and preliminary analysis of in vitro activity against Tritrichomonas foetus. *Eur. J. Med. Chem.* **2014**, *74*, 657–663. [CrossRef]
30. Gupta, N.; Tak, R.; Nazish, M.; Jakhar, A.; Khan, N.-u.H.; Kureshy, R.I. Copper(II) Triflate Catalyzed Regioselective and Enantioselective Propargylation of Isatin Derivatives by Using Allenylboronic Acid Pinacol Ester. *Eur. J. Org. Chem.* **2018**, *2018*, 1384–1392. [CrossRef]
31. Wang, Y.; Wang, S.; Shan, W.; Shao, Z. Direct asymmetric N-propargylation of indoles and carbazoles catalyzed by lithium SPINOL phosphate. *Nat. Commun.* **2020**, *11*, 226. [CrossRef] [PubMed]
32. Pirrung, M.C.; Pansare, S.V.; Sarma, K.D.; Keith, K.A.; Kern, E.R. Combinatorial Optimization of Isatin-β-Thiosemicarbazones as Anti-poxvirus Agents. *J. Med. Chem.* **2005**, *48*, 3045–3050. [CrossRef] [PubMed]
33. Vine, K.L.; Matesic, L.; Locke, J.M.; Ranson, M.; Skropeta, D. Cytotoxic and anticancer activities of isatin and its derivatives: A comprehensive review from 2000–2008. *Anti-Cancer Agents Med. Chem.* **2009**, *9*, 397–414. [CrossRef] [PubMed]