Synthesis and DFT studies of novel aminoimidazodipyridines using 2-(3H-imidazo[4,5-b]pyrid-2-yl)acetonitrile as an efficient key precursor

Ahmed F. Darweesh, a Nesma A. Abd El-Fatah, a Samir A. Abdel-Latif, b Ismail A. Abdelhamid, a* Ahmed H. M. Elwahy a* and Mostafa E. Salem a

aDepartment of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt
bDepartment of Chemistry, Faculty of Science, Helwan University, Cairo 11795, Egypt
Email: ismail_shafy@yahoo.com, elwahy@hotmail.com

Abstract

Novel 9-aminoimidazo[1,2-a:5,4-b']dipyridine-6,8-dicarbonitriles were prepared via the Michael addition reaction of readily accessible 2-(3H-imidazo[4,5-b]pyrid-2-yl)acetonitrile with arylidenemalononitriles. The regioselectivity of the reaction was supported by theoretical calculations at the DFT level. In contrast, the reaction of the appropriate bis-arylidenemalononitrile with 2-(3H-imidazo[4,5-b]pyrid-2-yl)acetonitrile under similar reaction conditions gave the corresponding bis[2-(3H-imidazo[4,5-b]pyrid-2-yl)acrylonitriles].

Keywords: 2-(3H-imidazo[4,5-b]pyrid-2-yl)acetonitrile, 9-aminoimidazo[1,2-a:5,4-b']dipyridine-6,8-dicarbonitrile, arylidenemalononitriles, bis[2-(3H-imidazo[4,5-b]pyrid-2-yl)acrylonitriles], DFT studies.
Introduction

Imidazo[4,5-b]pyridines are important classes of heterocyclic compounds that possess diverse pharmacological properties including anticancer, antimicrobial, anti-inflammatory, and antiviral activities. Moreover, N-fused polyheterocycles display also a wide range of biological activities. In particular, imidazo[1,2-a:5,4-b']dipyridines exhibit interesting anticancer and antiviral activities. Some examples of biologically active compounds containing an imidazo[1,2-a:5,4-b']dipyridine such as (CF02334) 1, a selective inhibitor of the cytopathic effect (CPE) caused by bovine viral diarrhea and anti-human prostate cancer are outlined in Figure 1. In addition, the development of simple and efficient synthetic routes to novel heterocyclic compounds represents a great challenge in organic synthesis. In this respect, the Michael addition reaction has attracted much attention in the last decades as an effective strategy for the synthesis of heterocycles and their fused derivatives under mild reaction conditions. Moreover, due to their promising nonlinear optical (NLO) properties, imidazo[1,2-a]pyridine and their corresponding fused derivatives have a diverse range of applications in material chemistry. In this respect, many of these derivatives have been used as multiple fluorescent chemosensors, in an electron transport layer of an organic light emitting device, as biomarkers of hypoxic tumor cells, and as a receptor in fluorescent high-affinity ligand in dopamine.

In connection with the increasing interest of adoption of new synthetic methods in drug discovery, and in continuation to our recent applications of carbon-Michael as well as aza-Michael addition reactions as powerful tools for the synthesis of nitrogen containing heterocycles and their corresponding bis-heterocycles, we report herein our investigation on the reactivity of 2-(3H-imidazo[4,5-b]pyrid-2-yl)acetonitrile towards arylidenemalononitriles and bis-aryldenemalononitriles aiming at synthesizing novel mono- and bis-imidazo[1,2-a:5,4-b']dipyridine-6,8-dicarbonitriles. In addition, a theoretical density functional theory (DFT) study aims to determine the more stable regioisomer of the two possible expected isomeric products from the mentioned reactions as well as to investigate the efficacy of the target compounds as suitable candidate for NLO material.

Results and Discussion

Synthesis

Previously, various methods have been reported for the synthesis of imidazo[1,2-a:5,4-b']dipyridines. Most of these methods depend mainly on the formation of 3-aminoimidazo[1,2-a]pyridines followed by their reaction with the appropriate reagents. In this respect, Takeda et al. synthesized imidazodipyridines 5 by the reaction of 3-aminoimidazo[1,2-a]pyridine 3 (R = H) with 2-chloroacrylonitrile 4 in nitrobenzene in the presence of
AlCl₃. Moreover, Desbois et al. synthesized imidazo[1,2-a:5,4-b']dipyridines via the reaction of 3-amino-2-formylimidazo[1,2-a]pyridine (R = CHO) with various aldehydes or ketones by Friedländer’s method (Scheme 1).

Algorithm 1. Reported Methods for the synthesis of imidazodipyridines 5 and 6.

Li et al. and Zhang et al. also reported on the utility of some imidazo[1,2-a]pyridin-3-amines as precursors for the synthesis of imidazo[1,2-a:5,4-b']dipyridines.

In searching for an expedient strategy for synthesis of imidazodipyridines, our attention focused on 2-(3H-imidazo[4,5-b]pyrid-2-yl)acetonitrile (10) as a precursor. Compound 10 was prepared via the solvent-free reaction of pyridine-2,3-diamine (7) with ethyl cyanoacetate (8) in an oil bath at 180-190 °C for 30 minutes (Scheme 2). The structure of compound 10 was supported by the presence of FTIR bands at 3410 and 2252 cm⁻¹ characteristic for v(N-H) and v(C≡N) groups, respectively. The ¹H NMR spectrum of compound 10 reveals the methylene group and the NH protons at δ 4.42 and 13.18, respectively. The data agreed with that previously reported for compound 10.


The reactivity of compound 10 towards substituted cinnaminitriles was then investigated. Compound 10 (a Michael donor) has two nucleophilic centers (NH group and CH₂) at which the Michael addition to the Michael acceptor 11 can initiate. Thus, two regioisomeric products are possible by the reaction of compound 10 with the activated double bond reagents 11 via routes A and B (Schemes 3 & 4). Route A involves the initial nucleophilic addition of CH₂ of compound 10 to β-carbon of the activated double bond of 11 followed by cyclization that involves the NH group to afford 9-amino-7-arylimidazo[1,2-a:5,4-b']dipyridine-6,8-dicarbonitrile 12 through intermediates 14 and 15 (Scheme 4). Route B encompasses the initial addition of the NH group of the compound 10 to the activated double bond of 11 followed by cyclization involving CH₂ of 10 to give 7-amino-9-arylimidazo[1,2-a:5,4-b']dipyridine-6,8-dicarbonitrile 13 through intermediates 16 and 17 (Scheme 4). The structures of the expected products 12 or 13 could not be determined based on spectral analyses as both of them give similar data. For example, the IR spectrum of the compound produced from the reaction of 10 with 11a showed the presence of amino group at v(N-H) 3456 and 3317 cm⁻¹ as well as characteristic nitrile band at v(C≡N) 2214 cm⁻¹. Its ¹H NMR spectrum revealed the amino group at δ 8.89 as a broad signal. Unfortunately, these data can agree with both structures 12 and 13.
Scheme 3. Synthesis of compounds 6a-e via reaction of 4 with cinnamionitriles.

Scheme 4. Expected routes (A and B) for the formation of regioisomeric products 12 and 13.

Route A that affords compounds 12 was approved based on literature similarities that indicated the superiority of the nucleophilicity of CH$_2$ over NH group. Further support for the formation of compound 12a was provided by an alternative synthesis via a three component reaction of 2-(3H-imidazo[4,5-b]pyrid-2-yl)acetonitrile 10 with both benzaldehyde (18) and malononitrile (19) in EtOH heated at reflux in the presence of catalytic piperidine (Scheme 6, Method B). Moreover, compound 12a was also obtained via the reaction of malononitrile (19) with a preheated mixture of benzaldehyde (18) and 2-(3H-imidazo[4,5-b]pyrid-2-yl)acetonitrile 10. In support of this viewpoint, we also isolated the Knoevenagel condensation product 2-(3H-imidazo[4,5-b]pyrid-2-yl)-3-phenylacrylonitrile (20) (Scheme 5, method C). The formation of 12a from the
reaction of 20 with 19, with identical physical and spectral data with that prepared from the reaction of 10 and 11a, supports the reaction proceeded via route A and not via route B.

Scheme 5. Alternative methods for the synthesis of compound 12a.

The regioselective formation of 12 was also supported by theoretical calculations at DFT level (cf. Molecular orbital calculations).

In searching for the optimal reaction conditions, the reaction was carried out in different solvents as well as in the presence of a variety of bases. Firstly, we tried EtOH as a solvent and DABCO, pyridine, KOH, TEA and piperidine as bases. Among the different bases, the use of piperidine gave the cleanest products and best yields. The reaction was also examined in different solvents including dioxane, dichloromethane, acetonitrile, water and DMF heated at reflux in each case. The reaction proceeded in most solvents but with different degrees of conversion; EtOH was the best solvent in terms of reaction time and yield. The reactions were completed in 3-5 h, while prolonged heating did not improve the reaction yield. On the other hand, no traces of products were obtained at room temperature. The reactivity of compound 10 towards heteromethylenemalononitriles was also investigated aiming at synthesizing novel imidazo[1,2-a:5,4-b’]dipyridines which are linked to heterocyclic moieties at position 7. Thus reaction of 10 with each of 2-[(1,3-diphenylpyrazol-4-yl)methylene]malononitrile (21a) and 2-[(1-phenyl-3-(thien-2-yl)-pyrazol-4-yl)methylene]-malononitrile (21b) afforded 9-amino-7-arylimidazo[1,2-a:5,4-b’]dipyridine-6,8-dicarbonitrile 22a and 22b, respectively, in good yields (Scheme 6).
Scheme 6. Synthesis of imidazo[1,2-α:5,4-b’]dipyridines 22a and 22b via reaction of compound 10 with heteromethylenemalononitriles.

Our study was extended to investigate the reactivity of 2-(3H-imidazo[4,5-b]pyrid-2-yl)acetonitrile (10) towards bis-arylidenemalononitrile 23 in a trial to prepare bis-9-amino-7-arylimidazo[1,2-α:5,4-b’]dipyridine-6,8-dicarbonitriles 24. Unfortunately, Michael addition of two equivalents of 2-(3H-imidazo[4,5-b]pyrid-2-yl)acetonitrile (10) to bis-arylidenemalononitriles did not lead to the formation of 24. Instead the reaction gave bis[2-(3H-imidazo[4,5-b]pyrid-2-yl)acrylonitriles] 25a-d (Scheme 7). Compounds 25 are assumed to form via the initial formation of the Michael adducts 26 which then decompose to afford 25 via elimination of malononitrile (Scheme 8). A similar pathway has been reported. The structures of compounds 25a-d were supported by comparison of their physical data with authentic samples prepared from the reaction of one equivalent of bis-aldehydes 27 with two equivalents of 2-(3H-imidazo[4,5-b]pyrid-2-yl)acetonitrile (10) in EtOH in the presence of catalytic piperidine (Scheme 9). The constitutions of compounds 25 were established based on spectral data. Thus, the 1H NMR spectrum of compound 25a as a representative example revealed two singlet signals at δ 4.63 and 8.59 for the OCH2 groups and the ylide H-atoms, respectively. Moreover, it revealed the NH group as broad singlet at 13.63 ppm.
Scheme 7. Attempted synthesis of bis-9-amino-7-arylimidazo[1,2-α:5,4-β']dipyridine-6,8-dicarbonitriles 24 via reaction of 10 with bis-arylidenemalononitrile 23.

Scheme 8. Plausible mechanism for the formation of 25a-d via reaction of 10 with bis-arylidenemalononitrile 23.

Scheme 9. Synthesis of compounds 25a-d by the reaction of one equivalent of bis-aldehydes 27 with two equivalents of 10.
Theoretical calculations

Geometry of compounds 12 and 13

Geometry structures of the expected products 12 and 13 and their intermediates 14 and 16 were optimized at the B3LYP/6-311G** level and the results are given in Table 1. The reaction of 10 with 11 can lead to the formation of the regioisomer 12, via intermediate 14 through the attack of the active CH₂ of 10 (C14) on CH groups of 11 (C12). On the other hand, the regioisomer 13 can arise via initial attack of NH of 10 on CH of 11 to give intermediate 16 as seen in Fig. 2 (cf. supporting information). The energy of regioisomer 13 was 7.15 kcal/mol higher than that of 12, i.e., the structure of 12 was more stable. Also, the intermediate 16 has energy of 5.52 kcal/mol higher than that of 14. Therefore, this study supports the regioselective formation of 12 from the reaction of 10 with 11. The planarity of 12 can be estimated from the values of the dihedral angles. Compound 12 has a non-planar structure where the phenyl ring rotates out of the plane. This is can be indicated from the dihedral angles of the phenyl ring attached to C13 and it has a lower chemical hardness. Large E₇ gaps are representative of the hardness of the molecule, while smaller E₇ gaps are representative for soft and reactive molecules. The accumulated data in Table 2 showed that the HOMO of 12 is less stable than that of the other compounds and has lower IP value. The electron affinities values are of the order: 10 < 12 < 11. The processed reactivity parameters are shown in Table 2 which revealed that compound 10 has the lowest η and minimum S values. This indicated that it has lower chemical hardness. The 3-D distribution of frontier MOs, HOMO and LUMO of 10, 11 and 12 are presented in Fig. 2. The calculated values of E_HOMO and E_LUMO of 12 are -6.1690 and -2.8478 eV, respectively, thus the energy gap value E₇ is 3.3212 eV. It can be regarded from Fig. 3 that the HOMO and LUMO of 12 are mainly allocated over the whole molecule. The partial frontier molecular orbital compositions and the energy levels of 12 in the ground state are recorded in Table 2 and Fig. 3.

Ground state properties and Global reactivity descriptors

The energy difference between the HOMO and LUMO, E₇, of compounds 10, 11 and 12 occur in the range 5.28-3.32 eV. The energy gap of compound 10 is the maximum (5.28 eV) while that for compound 12 has the minimum (3.32 eV) value (Table 2). As a result, charge transfer and polarization can easily occur with more reactivity within 12 than 10 and 11. The electronegativity, χ, chemical hardness, η, global softness, S, chemical potential, π, were calculated using HOMO and LUMO energies and were recorded in Table 2, Fig. 3 (cf. supporting information). Compound 10 has the lowest η and maximum S value which means that the charge transfer occurs easily in this compound and it has a lower chemical hardness. Large E₇ gaps are representative of the hardness of the molecule, while smaller E₇ gaps are representative for soft and reactive molecules. The calculated values of E_HOMO and E_LUMO of 12 are -6.1690 and -2.8478 eV, respectively, thus the energy gap value E₇ is 3.3212 eV. It can be regarded from Fig. 3 that the HOMO and LUMO of 12 are mainly allocated over the whole molecule. The partial frontier molecular orbital compositions and the energy levels of 12 in the ground state are recorded in Table 2 and Fig. 3.

Table 2. Total energy, energy of HOMO and LUMO, energy gap, of 10, 11, 12, 13, 14 and 16 using B3LYP/6-311G**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>E₇, eV</td>
<td>-14350</td>
<td>-13436</td>
<td>-27762</td>
<td>-27744</td>
<td>-27771</td>
<td>-27771</td>
</tr>
<tr>
<td>E_HOMO, eV</td>
<td>-6.7891</td>
<td>-7.3929</td>
<td>-6.1690</td>
<td>-5.9867</td>
<td>-6.8653</td>
<td>-6.9795</td>
</tr>
<tr>
<td>E_LUMO, eV</td>
<td>-1.5150</td>
<td>-3.0926</td>
<td>-2.8478</td>
<td>-3.2776</td>
<td>-1.7789</td>
<td>-1.8170</td>
</tr>
<tr>
<td>E₇, eV</td>
<td>5.2741</td>
<td>4.3003</td>
<td>3.3212</td>
<td>2.7091</td>
<td>5.0864</td>
<td>5.1625</td>
</tr>
</tbody>
</table>
The frequency calculations for compound 12a (Figure 4, cf. supporting information) were performed using B3LYP/6-31G(d,p). The data obtained are comparable with that theoretically calculated (Exp. 3456, 3317, 2214; Calc. 3470, 3240, 2212 cm⁻¹) cf. experimental section. TD-DFT calculations for compound 12a (Figure 5, cf. supporting information) were brought out at the same level of theory [B3LYP/6-31G(d,p)] to clarify the origin of the electronic spectra, using the polarizable continuum solvation method, PCM, PCM-TD-DFT. The theoretical spectrum of 12a is characterized by five bands at 361 (3.4316 eV), 308 (4.0224 eV), 286 (4.3248 eV), 262 (4.7280 eV) and 245 nm (5.0405 eV). Theoretical IR and UV spectra of 12a using B3LYP6-31G(d,p) are mentioned in supplementary material.

Non-linear optical properties (NLO)
The circulation of the atomic charges in the chelates is also valuable in the determination of the magnitude and direction of the moment vector which depends on the centers of negative and positive charges. The dipole moment, the mean polarizability, the anisotropy of the polarizability and the first-order hyperpolarizability for compounds 10, 11 and 12 were calculated using the same level and the obtained values are tabulated in Table 3. The table also includes the experimental values of urea. The considered dipole moment values of 10, 11 and 12 in the gas phase are 4.4076, 6.6808 and 5.3942 D, respectively. The analyzed values of the polarizability of 10, 11 and 12 have the range 1.09-7.02×10⁻²⁴ (esu). Compound 11 has the lowest calculated value and 12 has 7.02×10⁻²⁴. Compared with urea as a reference substance, all the studied chelates have higher polarizability and first-order hyperpolarizability. The polarizabilities and first-order hyperpolarizabilities are reported in atomic units (a.u.), the calculated values have been changed into electrostatic units (esu) using conversion factor of 0.1482×10⁻²⁴ esu for α and 8.6393×10⁻³³ esu for β. Urea is used as standard example in non-linear optical studies. In this study, urea is chosen as a reference material as there were no experimental values of NLO properties for the new derivatives. The extent of the molecular hyperpolarizability (〈β〉) is one of the key factors in non-linear optical system. The calculated (〈β〉) values for compounds 10, 11 and 12 are ~6, ~60, and ~6, times greater than that of urea, respectively. Therefore, all the studied compounds reveal considerable polarizability and first-order hyperpolarizability and are projected to be successful encouraged for NLO materials.

Conclusions
We developed a simple and an efficient method for the preparation of novel 9-aminoimidazo[1,2-a:5,4-b']dipyridine-6,8-dicarbonitriles via the Michael addition reaction that involves 2-(3H-imidazo[4,5-b]pyrid-2-yl)acetonitrile (as Michael donor) and the appropriate arylidenemalononitriles (as Michael acceptor). Also, we managed to synthesize bis[2-(3H-imidazo[4,5-b]pyrid-2-yl)acrylonitriles] through the reaction of 2-(3H-imidazo[4,5-b]pyrid-2-yl)acetonitrile with bis-arylidenemalononitriles under similar reaction conditions. The theoretical calculations were carried out using Gaussian 09 W package with Gauss View 5. The analysis includes bond lengths, bond angles, molecular electrostatic potential maps, description of the important frontier molecular orbital surfaces of the compounds. The optimized molecular structure of the compounds was obtained at B3LYP/6-311G**. The regioisomer 13 has higher energy than that of 12. This gives further confirmation for the formation of the more stable regioisomer 12. The polarizability and hyperpolarizabilities parameters of the compounds indicated that they are suitable candidate for NLO material.
Experimental Section

General. Melting points were determined in open glass capillaries with a Gallenkamp apparatus. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3-300 and Shimadzu FTIR 8101 PC infrared spectrophotometer. NMR spectra were recorded using a Varian Mercury VXR-300 NMR spectrometer or Bruker Ultrashield 400 MHz or Ascend 400 MHz (1H: 300 or 400 MHz, 13C: 75 or 100.6 MHz) instruments using DMSO-d6 as solvent. Mass spectra (EI) were obtained at 70 eV using a type Shimadzu GCMQP 1000 EX Spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 microanalyser at the Microanalytical Center of Cairo University. Compounds 1036, 1137, 23a-d38 and 27a-d38 were prepared according to the literature.

General procedure for the synthesis of 9-amino-7-substituted imidazo[1,2-a:5,4-b']dipyridine-6,8-dicarbonitrile 12a-e and 22a,b

Method A. To a mixture of appropriate arylidene malononitrile 11a-e, 21a or 21b (1 mmol) and 2-(3H-imidazo[4,5-b]pyrid-2-yl)acetonitrile (10) (1 mmol, 158 mg) in absolute EtOH (15 mL) was added piperidine (1 mmol, 110 μL), and the mixture was heated at reflux for 3-5 h. The crude solid was isolated and recrystallized from EtOH/DMF to give 12a-e and 22a,b, respectively.

For compound 12a:

Method B. To a mixture of benzaldehyde (18) (1 mmol, 106 mg), malononitrile (19) (1 mmol, 66 mg) and 2-(3H-imidazo[4,5-b]pyrid-2-yl)acetonitrile (10) (1 mmol, 158 mg) in absolute EtOH (25 mL) was added piperidine (1 mmol, 110 μL), and the reaction mixture was heated at reflux for 5 h. The crude solid was isolated and recrystallized from DMF/EtOH (25:75) to give 12a.

Method C. A mixture of 2-(3H-imidazo[4,5-b]pyrid-2-yl)-3-phenylacrylonitrile (20) (1 mmol, 246 mg) and malononitrile (19) (1 mmol, 66 mg) in absolute EtOH (15 mL) was added piperidine (1 mmol, 110 μL), and the mixture was heated at reflux for 3 h. The crude solid was isolated and recrystallized from DMF/EtOH (25:75) to give 12a.

9-Amino-7-phenylimidazo[1,2-a:5,4-b']dipyridine-6,8-dicarbonitrile (12a). Brown crystals, (method A (288 mg, 93%); method B (263 mg, 85%); method C (273 mg, 88%); mp > 300 °C; IR (KBr) ν (Exp. 3456, 3317, 2214; Calc. 3470, 3240, 2212) cm⁻¹; 1H NMR (400 MHz, DMSO-d6) δ 7.41-7.46 (m, 5H, ArH), 7.62 (m, 1H, pyridine-H), 7.31-7.33 (m, 1H, pyridine-H); 13C NMR (100 MHz, DMSO-d6) δ 78.7, 115.9, 116.2, 117.2, 121.8, 123.6, 129.2, 130.7, 135.2, 137.8, 142.1, 148.4, 149.7, 152.8, 154.6, 156.6; MS m/z (%) 310 (M⁺). Anal. Calcd for C18H10N6: C, 69.67; H, 3.25; N, 27.08. Found: C, 69.52; H, 3.07; N, 26.97%.

9-Amino-7-(4-chlorophenylimidazo[1,2-a:5,4-b']dipyridine-6,8-dicarbonitrile (12b). Brown crystals (279 mg, 81%); mp > 300 °C; IR (KBr) ν 3454, 3317, 2214 cm⁻¹; 1H NMR (400 MHz, DMSO-d6) δ 7.41-7.46 (m, 1H, pyridine-H), 7.62-7.72 (m, 5H, ArH), 8.69-8.71 (m, 1H, pyridine-H), 8.93 (br. s, 2H, NH2), 9.00-9.02 (m, 1H, pyridine-H); 13C NMR (100 MHz, DMSO-d6) δ 78.7, 115.9, 116.1, 117.3, 121.8, 123.6, 129.3, 131.1, 133.4, 135.6, 144.4, 148.5, 149.6, 152.8, 153.3, 156.6; MS m/z (%) 344 (M⁺). Anal. Calcd for C18H9ClN6: C, 67.41; H, 2.63; N, 24.38. Found: C, 62.46; H, 2.44; N, 24.28%.

9-Amino-7-(p-tolylimidazo[1,2-a:5,4-b']dipyridine-6,8-dicarbonitrile (12c). Pale brown crystals (282 mg, 87%); mp > 300 °C; IR (KBr) ν 3456, 3317, 2214 cm⁻¹; 1H NMR (400 MHz, DMSO-d6) δ 7.41-7.52 (m, 5H, ArH & pyridine-H), 8.68-8.69 (m, 1H, pyridine-H), 8.82 (br. s, 2H, NH2), 8.99-9.02 (m, 1H, pyridine-H); 13C NMR (100 MHz, DMSO-d6) δ 121.9, 123.5, 129.1, 129.7, 132.3, 140.5,
148.3, 149.9, 153.0, 154.6, 156.7; MS m/z (%) 324 (M⁺). Anal. Calcd for C₁₉H₁₂N₆: C, 70.36; H, 3.73; N, 25.91. Found: C, 70.15; H, 3.55; N, 25.79%.

9-Amino-7-(4-methoxyphenyl)imidazo[1,2-a:5,4-b']dipyrroline-6,8-dicarbonitrile (12d). Pale brown crystals (309 mg, 91%); mp > 300 °C; IR (KBr) ν 3456, 3294, 2214 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 3.88 (s, 3H, OCH₃), 7.17 (d, 2H, ArH, J 8.8 Hz), 7.42-7.45 (m, 1H, pyridine-H), 7.58 (d, 2H, ArH, J 8.4 Hz), 8.69-8.70 (m, 1H, pyridine-H), 8.81 (br. s, 2H, NH₂), 8.99-9.01 (m, 1H, pyridine-H); ¹³C NMR (100 MHz, DMSO-d₆) δ 55.7, 79.0, 114.5, 116.2, 116.4, 117.1, 121.8, 123.6, 127.1, 130.9, 148.0, 149.9, 152.9, 154.3, 156.7, 161.2; MS m/z (%) 340 (M⁺). Anal. Calcd for C₁₉H₁₂N₆O: C, 67.05; H, 3.55; N, 24.69. Found: C, 66.89; H, 3.32; N, 24.50%.

9-Amino-7-[benzo[d][1,3]dioxol-5-yl]imidazo[1,2-a:5,4-b']dipyrroline-6,8-dicarbonitrile (12e). Brown crystals (315 mg, 89%); mp > 300 °C; IR (KBr) ν 3457, 3284, 2214 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 6.19 (s, 2H, OCH₂O), 7.10-7.21 (m, 3H, ArH), 7.41-7.44 (m, 1H, pyridine-H), 8.68-8.69 (m, 1H, pyridine-H), 8.83 (br. s, 2H, NH₂), 8.99-9.01 (m, 1H, pyridine-H); ¹³C NMR (100 MHz, DMSO-d₆) δ 78.9, 102.3, 109.0, 109.5, 116.1, 116.4, 117.1, 121.8, 123.5, 123.7, 128.6, 147.7, 148.4, 149.3, 149.8, 152.8, 154.1, 156.7; MS m/z (%) 354 (M⁺). Anal. Calcd for C₁₉H₁₆N₆O₂: C, 64.41; H, 2.84; N, 23.72. Found: C, 64.25; H, 2.64; N, 23.58%.

9-Amino-7-(1,3-diphenyl-1H-pyrrozol-4-yl)imidazo[1,2-a:5,4-b']dipyrroline-6,8-dicarbonitrile (22a). Yellow crystals (366 mg, 81%); mp > 300 °C; IR (KBr) ν 3448, 3047, 2206 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 7.26-8.8 (m, 15H, ArH, NH₂ & pyridine-H), 9.27 (s, 1H, pyrazole-5-H); MS m/z (%) 452 (M⁺). Anal. Calcd for C₂₂H₂₀N₈: C, 71.67; H, 3.56; N, 24.76. Found: C, 71.39; H, 3.45; N, 24.57%.

9-Amino-7-[1-phenyl-3-(thien-2-yl)-1H-pyrrozol-4-yl]imidazo[1,2-a:5,4-b']dipyrroline-6,8-dicarbonitrile (22b). Brown crystals (325 mg, 71%); mp > 300 °C; IR (KBr) ν 3535, 3332, 2214 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 6.98-9.12 (m, 13H, ArH, NH₂, thiophene-H & pyridine-H), 9.25 (s, 1H, pyrazole-H); MS m/z (%) 458 (M⁺). Anal. Calcd for C₂₅H₂₄N₈S: C, 65.49; H, 3.08; N, 24.44; S, 6.99. Found: C, 65.39; H, 2.95; N, 24.23; S, 6.76%.

Synthesis of 2-(3H-imidazo[4,5-b]pyrid-2-yl)-3-phenylacrylonitrile (20)

To a mixture of benzaldehyde (18) (106 mg, 1 mmol) and 2-(3H-imidazo[4,5-b]pyrid-2-yl)acetonitrile (10) (1 mmol, 110 mg) in absolute EtOH (15 mL) was added piperidine (1 mmol, 110 μL), and the mixture was heated at reflux for 3 h. The crude solid was isolated and recrystallized from DMF/EtOH (25:75) to give 20 as brown crystals, 234 mg (95%); mp 260-262 °C; IR (KBr) ν 3435, 3055, 2214, cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 7.30 (dd, 1H, pyridine-3-H, J₁ 8.0 Hz, J₂ 4.8 Hz), 7.61-8.41 (m, 7H, ArH, pyridine-2-H & pyridine-4-H), 8.44 (s, 1H, =CH-Ph), 13.98 (s, 1H, NH); MS m/z (%) 246 (M⁺). Anal. Calcd for C₁₅H₁₀N₄: C, 73.16; H, 4.09; N, 22.75. Found: C, 72.93; H, 3.97; N, 22.55%.

General procedure for the synthesis of bis(2-(3H-imidazo[4,5-b]pyrid-2-yl)acrylonitrile) derivatives 25a-d

To a mixture of appropriate bis(arylidenedemalononitrile) 23a-d (1 mmole) and 2-(3H-imidazo[4,5-b]pyrid-2-yl)acetonitrile (10) (2 mmol, 316 mg) in absolute EtOH (15 mL) was added piperidine (2 mmol, 110 μL), and the mixture was heated at reflux for 2 h. The crude solid was isolated and recrystallized from DMF/EtOH (25:75) to give 25a-d, respectively.

2,2'-(3,3'-[Ethane-1,2-diylbis(oxy)]bis[2,1-phenylene])bis[2-(3H-imidazo[4,5-b]pyrid-2-yl)acrylonitrile] (25a). Yellow crystals (478 mg, 87%); mp 259-262 °C; IR (KBr) ν 3433, 3047, 2970, 2214, 1249 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 4.63 (s, 4H, OCH₂), 7.06-8.38 (m, 14H, ArH & pyridine-H), 8.59 (s, 2H, 2CH), 13.63 (br. s, 2H, NH); ¹³C NMR (100 MHz, DMSO-d₆) δ 68.1, 103.4, 104.5, 113.8, 114.6, 116.3, 119.0, 121.6, 122.3, 125.0, 128.9, 133.9, 142.4, 145.1, 149.6, 157.8; MS m/z (%) 550 (M⁺). Anal. Calcd for C₃₂H₂₂N₈O₂: C, 69.81; H, 4.03; N, 20.35. Found: C, 69.55; H, 3.90; N, 20.18%.

2,2'-(3,3'-[Propane-1,3-diylbis(oxy)]bis[2,1-phenylene])bis[2-(3H-imidazo[4,5-b]pyrid-2-yl)acrylonitrile] (25b). Pale yellow crystals (508 mg, 90%); mp 268-270 °C; IR (KBr) ν 3417, 3055, 2954, 2214, 1249 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 2.39 (br. s, 2H, CH₂), 4.38 (t, 4H, OCH₂, J 6.4 Hz), 7.07-8.40 (m, 14H, ArH &
pyridine-H), 8.62 (s, 2H, 2CH), 13.34 (br. s, 2H, 2NH); MS m/z (%) 564 (M'). Anal. Calcd for C_{33}H_{24}N_{8}O_{2}: C, 70.20; H, 4.28; N, 19.85. Found: C, 69.92; H, 4.10; N, 19.64%.

2,2'-(3,3'-[Propane-1,3-diylbis(oxy)]bis[4,1-phenylene])bis[2-(3H-imidazo[4,5-b]pyrid-2-yl)acrylonitrile] (25c). Yellow crystals (468 mg, 94%); mp 272-274 °C; IR (KBr) ν 3446, 3047, 2954, 2214, 1257 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 2.25-2.33 (m, 2H, CH₂), 4.30 (t, 4H, OCH₂), 7.21-8.38 (m, 14H, ArH & pyridine-H), 8.38 (s, 2H, 2CH), 12.38 (br. s, 2H, 2NH); ¹³C NMR (100 MHz, DMSO-d₆) δ 28.8, 65.1, 99.3, 115.5, 116.0, 116.8, 119.0, 125.6, 132.3, 132.6, 145.0, 146.8, 150.7, 162.0; MS m/z (%) 564 (M'). Anal. Calcd for C_{33}H_{24}N_{8}O_{2}: C, 70.20; H, 4.28; N, 19.85. Found: C, 70.44; H, 4.30; N, 19.74%.

2,2'-(3,3'-[Butane-1,4-diylbis(oxy)]bis[4,1-phenylene])bis[2-(3H-imidazo[4,5-b]pyrid-2-yl)acrylonitrile] (25d). Yellow crystals (534 mg, 94%); mp 267-270 °C; IR (KBr) ν 3446, 3047, 2954, 2214, 1257 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 1.93 (br. s, 4H, 2CH₂), 3.4 (br. s, 2H, 2NH); 4.18 (br. s, 4H, 2CH₂), 7.10-8.37 (m, 14H, ArH & pyridine-H), 8.37 (s, 2H, 2CH), MS m/z (%) 578 (M'). Anal. Calcd for C_{34}H_{26}N_{8}O_{2}: C, 70.58; H, 4.53; N, 19.37. Found: C, 70.44; H, 4.30; N, 19.22%.

**Computational Details**

Due to the absence of single crystal X-ray structure analysis and to attain the molecular conformation of compounds 10, 11 and 12, energy minimization analyses were done by means of Gaussian-09W software package.³⁹ The ground state geometrical structure of the three compounds were optimized using DFT method with the B3LYP exchange correlation functional approach.⁴¹ The basis set 6-311G** was applied for C, H and N atoms.⁴² Without any symmetry constraints, the geometry of the investigated systems was totally optimized in gas-phase. Gauss View 5 software was used to create figures of molecular orbitals (MOs). The quantum chemical parameters of the studied compounds are gained from calculations as energies of the lowest unoccupied molecular orbital (E_{LUMO}), the highest occupied molecular orbital (E_{HOMO}), HOMO-LUMO energy gap, E₉, absolute electronegativities, χ, chemical potentials, π, absolute hardness, η, absolute softness, σ, global electrophilicity, ω, global softness, S, and additional electronic charge, ΔN_{max}. These parameters are calculated using the following equations:⁴⁴ E₉ = E_{LUMO} - E_{HOMO}, χ = -E_{HOMO} + E_{LUMO}/2, η = E_{LUMO} - E_{HOMO}/2, σ = 1/η, π = -χ, S = 1/2η, ω = π²/2η and ΔN_{max} = -π/η. The spin density difference map calculations were also achieved to clarify their optical properties. Natural bond orbital (NBO) calculations were done with the NBO code contained in Gaussian 09 to understand different second order interaction between the filled orbital of one subsystem and empty orbital of another subsystem which is the calculate of the molecular delocalization or hyperconjugation. The total static dipole moment (μ), the mean polarizability <α>, the anisotropy of the polarizability, Δα and the mean first-order hyperpolarizability, <β> using the x, y, z components were calculated by using the following equations at B3LYP/ GENECP level of theory:⁴⁶

\[
\mu = (\mu_x^2 + \mu_y^2 + \mu_z^2)^{1/2},
\]

\[
\langle \alpha \rangle = 1/3 (\alpha_{xx} + \alpha_{yy} + \alpha_{zz}),
\]

\[
\Delta \alpha = ((\alpha_{xx} - \alpha_{yy})^2 + (\alpha_{yy} - \alpha_{zz})^2 + (\alpha_{zz} - \alpha_{xx})^2)/2)^{1/2},
\]

\[
\langle \beta \rangle = (\beta_x^2 + \beta_y^2 + \beta_z^2)^{1/2},
\]

where

\[
\beta_x = \beta_{xxx} + \beta_{xyy} + \beta_{xzz},
\]

\[
\beta_y = \beta_{yyy} + \beta_{xxy} + \beta_{yyz},
\]

\[
\beta_z = \beta_{zzz} + \beta_{zxz} + \beta_{zyy}.
\]
Supplementary Material

$^1$H and $^{13}$C NMR spectra for compounds 12a-e; 20; 22a,b and 25a-d and the tables and figures for the calculation section can be found via the “Supplementary Content” section of this article’s webpage.

References


https://doi.org/10.1002/jhet.3072

https://doi.org/10.1016/S0065-2725(08)00201-8

https://doi.org/10.1016/j.tet.2015.12.024

https://doi.org/10.1016/j.tet.2017.01.047

https://doi.org/10.3184/030823401103169540

https://doi.org/10.1007/s00706-017-2040-7

https://doi.org/10.3987/COM-16-13441

https://doi.org/10.1002/jhet.2867

https://doi.org/10.1055/s-0037-1609967

https://doi.org/10.1002/ardp.202000069

https://doi.org/10.1248/cpb.26.2924

https://doi.org/10.3987/COM-05-10354

https://doi.org/10.1002/adsc.202000553

https://doi.org/10.1016/j.ejmech.2015.03.050

https://doi.org/10.1016/j.ccl.2009.11.034

https://doi.org/10.1016/j.bmc.2011.05.013
   https://doi.org/10.1080/00397911.2020.1784436
   https://doi.org/10.1016/j.tet.2015.01.026
   https://doi.org/10.1016/S0167-577X(02)00680-8
   https://doi.org/10.1021/acs.jmedchem.6b01641
   https://doi.org/10.1080/00397911.2019.1620283
   https://doi.org/10.1002/jhet.2584
   https://doi.org/10.1063/1.464913
   https://doi.org/10.1103/PhysRevB.37.785
   https://doi.org/10.1063/1.447079
   https://doi.org/10.1016/j.saa.2014.02.037
   https://doi.org/10.1039/B314148A
   https://doi.org/10.1016/j.saa.2011.06.037

This paper is an open access article distributed under the terms of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/)