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Article

Deep Eutectic Solvent (DES)-Mediated One-Pot Multicomponent Green Approach for Naphthalimide-Centered Acridine-1,8-dione Derivatives and Their Photophysical Properties

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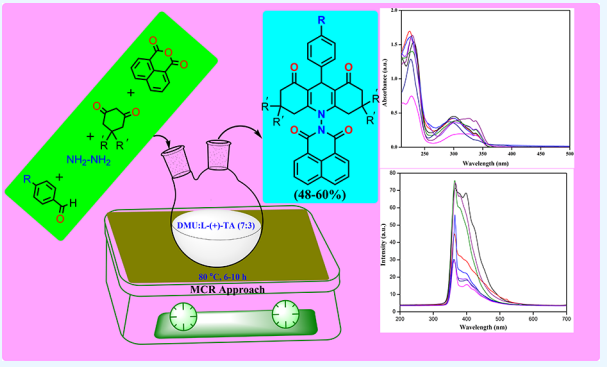
ABSTRACT: An efficient and green methodology to assemble various functionalized naphthalimide-centered acridine-1,8-dione derivatives involving a one-pot multicomponent protocol has successfully been developed. Herein, a variety of aromatic aldehydes, 1,3-diketones, 1,8-naphthanoic anhydride, and hydrazine hydrate have been condensed under a reusable, inexpensive, and biodegradable deep eutectic solvent (DES) of *N*,*N*′-dimethyl urea and L-(+)-tartaric acid to obtain the desired targets under operationally mild reaction conditions with outstanding conversions. Strikingly, in this strategy, the DES plays a dual role of a catalyst and solvent and was recycled efficiently in four consecutive runs with no substantial drop in the yield of the desired product. Interestingly, the easy recovery and high reusability of the DES make this simple yet efficient protocol environmentally desirable. Moreover, the preliminary photophysical properties of thus-prepared valuable molecules have also been investigated by ultraviolet−visible (UV−vis) and fluorescence spectroscopy.



INTRODUCTION

Multicomponent reactions (MCRs) entail three or more entities in a single flask, thereby offering the desired product with high atom economy and step economy.[1,2] These simple yet powerful approaches are acknowledged as the key development in the tool box of synthetic chemists and have established a central platform in green and/or sustainable chemistry in a way of reporting delicate chemical glitches in an eco-friendly manner.[3,4] Nowadays, MCRs have become prevailing tools in drug discovery,[5] medicinal chemistry,[6] natural product synthesis,[7] combinatorial chemistry,[8] polymeric chemistry,[9] and agrochemistry.[10] In the arena of medicinal chemistry and drug discovery, naphthalimide- and bis-naphthalimide-based DNA-intercalating agents such as mitonafide (**1**), amonafide (**2**), LU 79553 (**3**), and DMP 840 (**4**) have exhibited noteworthy antitumour activity in preclinical and clinical trials (Figure 1).[11−13] On the other hand, acridine and bis-acridine analogues such as imidazoacridinone C-1311 (**5**), WMC-26 (**6**), and *N*-[(2-dimethylamino)-ethyl]acridine-4-carboxamide (DACA, **7**) by virtue of notable anticancer activity have also captured significant attention of pharmaceutical and medicinal chemists (Figure 1).[14−16] It is thus anticipated that the conjugate molecular systems comprising naphthalimide and acridine moieties might be of high therapeutic and biological value.

To accomplish the successful synthesis of such conjugate molecular architectures, Chandramouli and teammates have recently revealed for the first time an ionic liquid-mediated procedure for the synthesis of naphthalimide-centered acridine-1,8-diones by the MCR strategy.[17] Noticeably, ionic liquids (ILs) in general are treated as greener reaction media, but unfortunately, they are not.[18] This is by virtue of the fact that ILs possess some severe issues, for instance, high viscosity, difficulty in their preparation, costlier, and environmentally unfriendly because of their generation from precarious starting materials encompassing conventional volatile organic solvents and corrosive catalysts.[19] Thus, there is vast urgency to assemble diverse functionalized naphthalimide-based acridine-1,8-dione derivatives using green approaches involving MCRs.

Among the diverse green and sustainable surrogates,[20−25] deep eutectic solvents (DESs), for the first time realized by Abbott's group in 2003, have been continuously drawing a lot of attention of researchers globally, which can be inspected by a flow of scientific papers appearing in the literature day by day.[26] The DESs in addition to exhibiting dual/triple features (solvent, catalyst, and/or reactant) in a reaction medium under consideration also display remarkable signatures including

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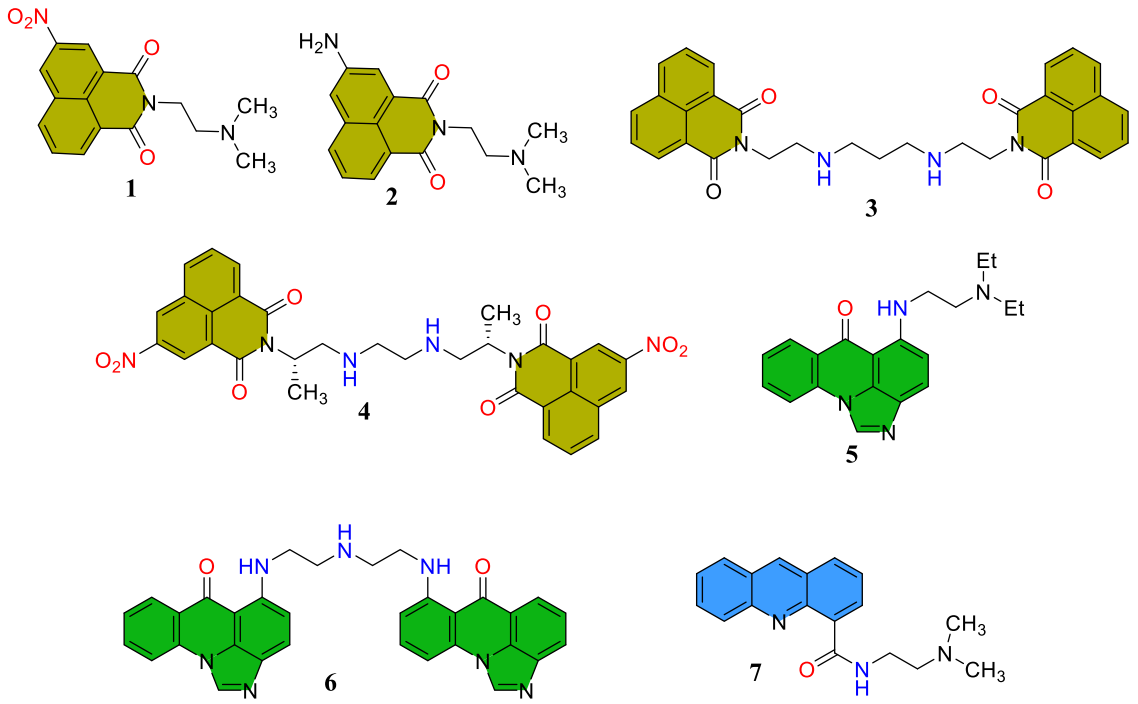
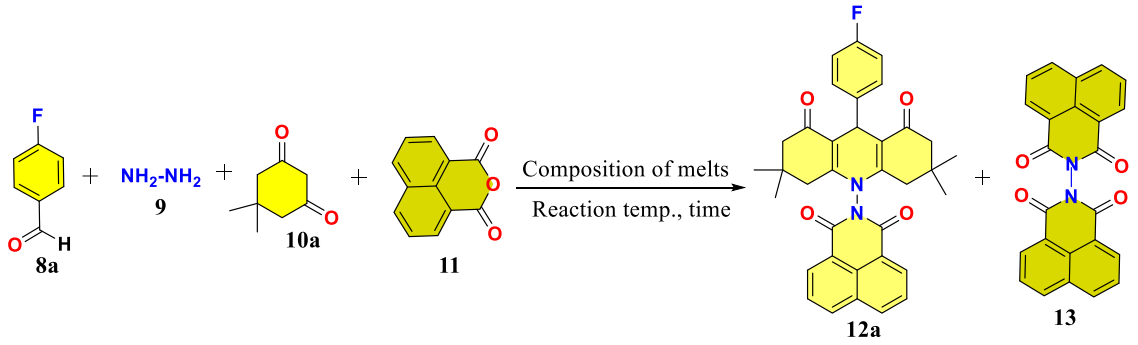


Figure 1. Some representative naphthalimide/bis-naphthalimide and acridine/bis-acridine derivatives of pharmaceutical relevance.

Table 1. Optimization of Reaction Conditions through the Usage of DESs for the Construction of a Naphthalimide−Acridine Conjugate Compound (12a)



entry	screening of DESs	reaction temp. (°C)	DES amount (g)	time (h)	%yield[a] (**12a**)
1	DMU/TA (7:3)	70	3	9	39
2	DMU/TA (7:3)	80	1	12	35
3	DMU/TA (7:3)	80	2	10	42
4	DMU/TA (7:3)	80	3	6	60
5	DMU/TA (7:3)	80	4	6	58
6	DMU/TA (7:3)	90	3	6	56
7	citric acid/mannitol/urea (3:2:5)	80	3	10	8
8	citric acid/DMU (2:3)	80	3	24	trace
9	ChCl/urea (1:2)	80	3	24	trace
10	ChCl/*p*TSA (1:2)	80	3	10	trace
11	ChCl/$ZnCl_2$ (1:2)	80	3	10	trace
12	ChCl/L-(+)-TA (1:2)	80	3	10	0

[a]Isolated yields after column chromatography; ChCl = choline chloride, *p*TSA = *p*-toluene sulfonic acid.

biodegradability, biocompatibility, atom economy, nonflammability, thermal stability, renewability, inexpensiveness, ease of handling, *etc.*[27−37] Taking the above-said and other, if any, amazing features of DESs into consideration and with our current research interest toward the development of green protocols for simple and interesting molecules using DESs,[38−47] herein, for the first time, we report a DES-mediated one-pot green synthesis of naphthalimide-centered acridine-1,8-dione derivatives through a multicomponent reaction of dimedone/cyclohexan-1,3-dione, hydrazine hydrate, 1,8-naphthanoic anhydride, and aromatic aldehydes. We believe that this useful eco-friendly methodology will open up new prospects for the construction of novel heterocyclic

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compounds in general and various interesting naphthalimide- and acridine-based conjugate molecular systems in particular.

RESULTS AND DISCUSSION

For the optimization of reaction conditions and also to check the feasibility of DESs for the desired MCR, a trial reaction between inexpensive and commercially accessible starting materials, *viz*. 4-fluorobenzaldehyde (**8a**), hydrazine hydrate (**9**), dimedone (**10a**), and 1,8-naphthanoic anhydride (**11**), was chosen as the model reaction to prepare a naphthalimide−acridine conjugate compound (**12a**). As can be examined from Table 1, among various tested DESs, 7:3 ratio of *N,N′*-dimethyl urea (DMU) and L-(+)-tartaric acid (TA) was found to be the best reaction medium at 80 °C (Table 1, entry 4). Noticeably, enhancing the temperature from 70 to 80 °C displays a substantial effect not only on the time of the reaction but also on the yield of the target compound **12a** (Table 1, entries 1 and 4). However, increasing the temperature beyond 80 °C leads to a slight drop in the yield of the desired conjugate compound **12a** (entries 4 and 6) without affecting the overall time of the test reaction. For the optimization of the amount of the desired DES (Table 1, entries 2−5), we witnessed a continuous enrichment in the yield of **12a** and reduction in the time of the desired reaction upon increasing the amount of DES from 1 to 3 g, whereas a further increase in the amount of the DES from 3 to 4 g does not show any favorable changes (Table 1, entry 5). Unfortunately, all attempts to achieve selectivity for the target conjugate compound **12a** in a model reaction failed when using the optimized 3 g of DES DMU/TA (7:3) at 80 °C, as we noticed the formation of the undesired product **13** (characterized by ^{1}H NMR) in a satisfactory yield (30%) along with some unidentified polar complex mixtures (observed by TLC). In the case of carbohydrate-based DESs such as citric acid/mannitol/urea (3:2:5) at 80 °C (Table 1, entry 7), we observed the formation of **12a** in a very low yield (8%). Similarly, with citric acid/DMU (2:3) (Table 1, entry 8), a trace amount of the required compound **12a** was isolated. Surprisingly, with the tested choline chloride (ChCl)-based DESs, either a trace amount of **12a** was noticed (Table 1, entries 8−11) or no desired compound **12a** was obtained (Table 1, entry 12). In all these cases, we observed some anonymous complex mixtures, detected in the TLC. To corroborate recyclability and reusability, the optimized DES DMU/TA (7:3) after the first run was sequestered from the reaction mixture *via* a liquid−liquid extraction method followed by aqueous layer evaporation.[48] The obtained DES was then dried under vacuum and reused in the next run to execute the model reaction. Interestingly, it was observed that the efficacy of the DES under similar reaction conditions to obtain **12a** was not considerably reduced even after four consecutive runs (Figure 2).

To show the substrate scope of this newly established green protocol, we intended to change the substituents at the *para* position of the benzene ring of the aromatic aldehydes (**8a−h**), so as to reveal their reactivity and selectivity toward desired product formation. In this direction, we have successfully assembled various functionalized naphthalimide−acridine conjugates (**12a−h**) in respectable yields (48−58%) by utilizing the optimized reaction conditions of the MCR revealed for the target compound **12a** (Scheme 1). Interestingly, from our experimentation, it was pointed out that the aromatic aldehydes (**8a−c**) consisting of electron-withdrawing groups (EWGs) at the *p*-position react faster with the substrates (**9, 10a**, and **11**) and lead to the synthesis of the desired corresponding conjugate compounds (**12a−c**) in good yields (55−60%) in a time period of 6 h (Scheme 1). On the other hand, aromatic aldehydes (**8e−g**) containing electron-donating groups (EDGs) at the *p*-position were found to react at slower rates under identical conditions and also offered the required products (**12e−g**) in comparatively lower yields (48−50%) in longer reaction times (8−10 h), as displayed in Scheme 1. Similar to the model reaction, formation of the undesired product (**13**) (25−30%) and unidentified complex mixtures (observed from TLC) was observed along with the anticipated products. The functionalized naphthalimide−acridine conjugates (**12a−h**) were already reported by Chandramouli and co-workers in better yields (64−93%) in a time period of 35−50 min using ionic liquids in a single step.[17] However, our newly developed DES-aided green protocol for these derivatives (**12a−h**) is cheap and environmentally more feasible. Finally, to our surprise, under the optimized reaction conditions, 7-(*tert*-butyl)pyrene-1-carbaldehyde (**14**) and *β*-formylated calix[4]pyrrole (**16**) failed to react (starting materials recovered) even after a prolonged reaction time at higher temperatures, and the reason for their ineffectiveness is still unclear (Scheme 2). To further extend the substrate scope of this newly developed DES-mediated green protocol, we changed the cyclic ketone counterpart with cyclohexan-1,3-dione (**10b**) and treated it with fluorobenzaldehyde (**8a**), hydrazine hydrate (**9**), and 1,8-naphthanoic anhydride (**11**) in the presence of DMU/TA (7:3) at 80 °C (Scheme 1). We were successful in obtaining a naphthalimide−acridine conjugate compound (**12i**) in a good yield (56%) within a time period of 6 h. Importantly, all the known synthesized compounds (**12a−h** and **13**) were confirmed by ^{1}H NMR spectra (Figures S1−S8 and S12) and melting points. The unknown compound (**12i**) was characterized through ^{1}H NMR,^{13}C NMR, and high-resolution mass spectrometry (HRMS) (Figures S9−S11)

To disclose the reactivity patterns of different functionalized aromatic aldehydes (**8a**, **8d**, and **8e**) with hydrazine hydrate (**9**), dimedone (**10a**), and 1,8-naphthanoic anhydride (**11**) *via*

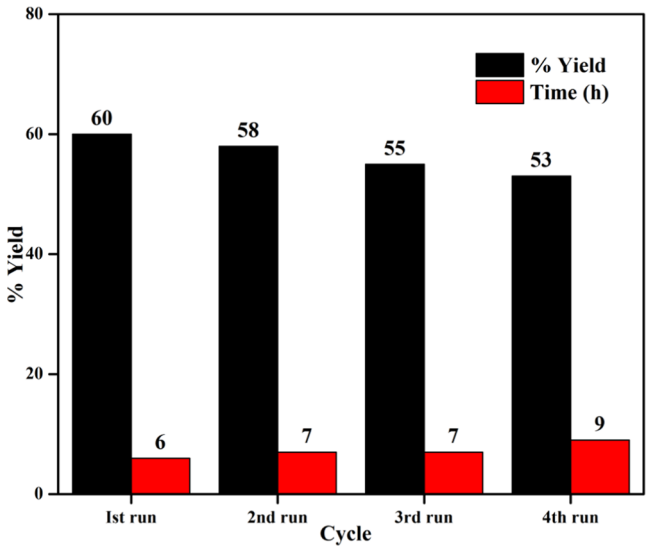

Figure 2. Bar graph displaying the recyclability efficacy of DMU/TA (7:3) for the synthesis of the target naphthalimide−acridine conjugate compound (**12a**).

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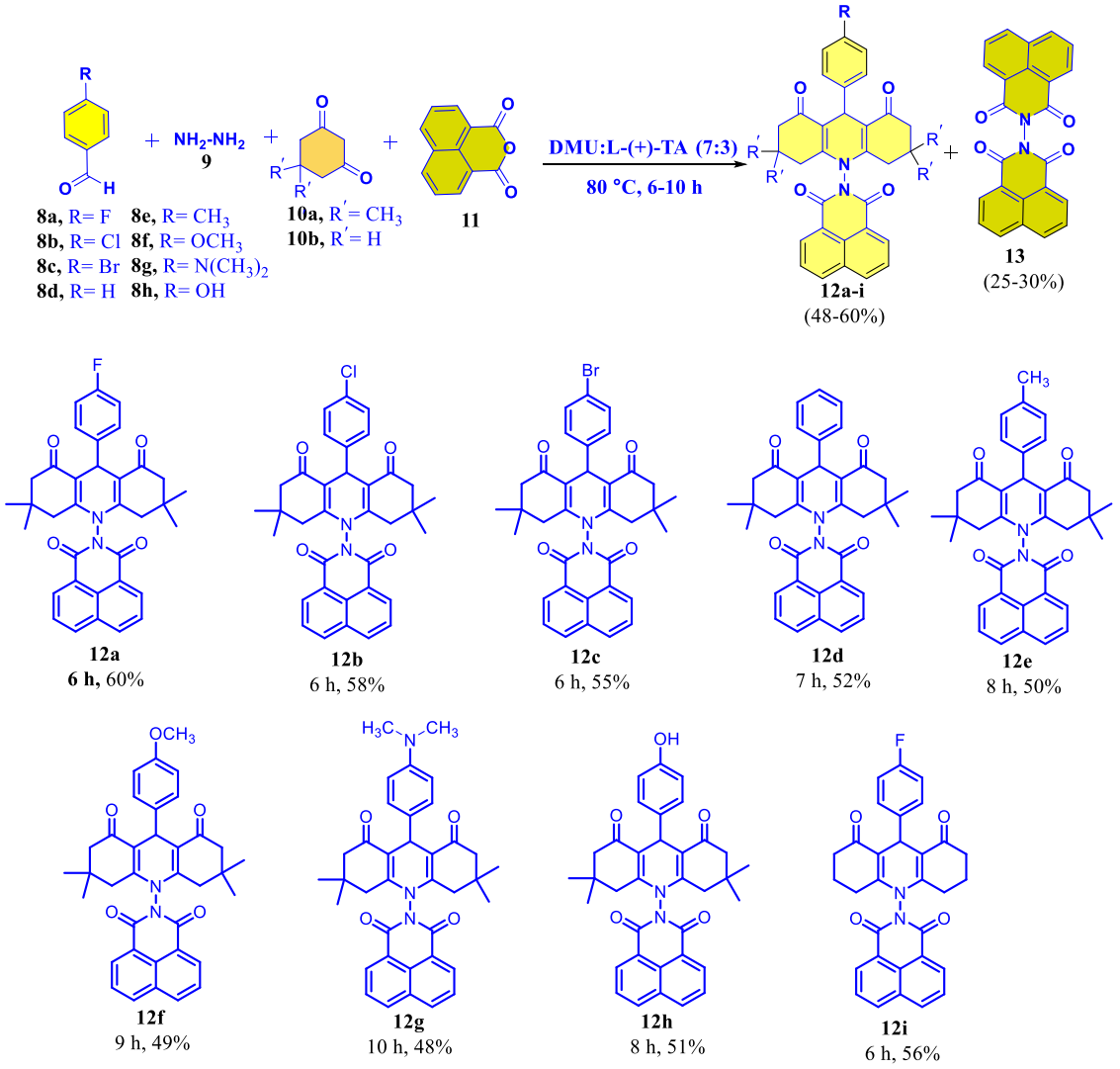
Scheme 1. Schematic Illustration of Various Functionalized Naphthalimide−Acridine Conjugate Compounds (12a−i) and Undesired Product (13) *via* DMU/TA (7:3) at 80 °C



the one-pot MCR approach, a competitive reaction was executed with an optimized DES (Scheme 3). It has been noticed that under optimized conditions, 4-fluorobenzaldehyde (**8a**) reacts faster in comparison to benzaldehyde (**8d**), followed by *p*-tolualdehyde (**8e**) (Scheme 3). Therefore, these outcomes are in agreement with the statement that aromatic aldehyde having EWGs reacts faster in comparison to aromatic aldehyde holding EDGs.

The plausible reaction mechanism of functionalized naphthalimide−acridine conjugate compounds (**12a−i**) *via* the DES DMU/TA (7:3) is illustrated in Scheme 4. First of all, the DES (**22**) is formed through H-bonding contacts between the carbonyl groups of DMU and hydroxyl groups of L-(+)-TA.[49] This DES becomes the source of protons and activates the carbonyl group of various aromatic aldehydes (**8a−h**). Subsequently, the nucleophilic attack of cyclic ketonic compound **24** (in the enol form) onto the carbonyl carbon of aromatic aldehydes (**8a−h**) occurs, leading to the formation of an intermediate **25**. Afterward, the intermediatory compound **25** was attacked by the imine-centered compound (Schiff base) **26** to offer the compound **27**, which on cyclization trailed by dehydration afforded the desired naphthalimide−acridine conjugate compounds (**12a−i**).[17]

Absorption and Emission Spectra. The absorption and emission spectra of the functionalized naphthalimide−acridine conjugates (**12a−h**) were recorded in 5×10^{-6} M solution of naphthalimide−acridine conjugates (**12a−h**) in pure methanol at ambient temperature (Figure 3). As can be inferred from Figure 3, all the compounds (**12a−h**) display absorption maxima at 224−232 nm. Moreover, these compounds also exhibit characteristic less-intense absorption bands between 280 and 349 nm, probably due to $\pi-\pi^*$ transitions. The reference naphthalimide−acridine conjugate compound (**12d**) reveals absorption maxima at 227 nm, a weak band at 301 nm, and two shoulders at 217 nm and 339 nm. On the other hand, the conjugate compound (**12a**) exhibited strong absorption maxima at 231 nm along with a less-intense band at 301 nm and two shoulders at 218 and 338 nm. The conjugate compounds (**12b, 12c**) offer a strong absorption band at 224−225 nm and two weak bands at 297 nm and 339−340 nm. On the other hand, the compounds (**12e−h**) showed high-intensity absorption bands between 226 and 229 nm and

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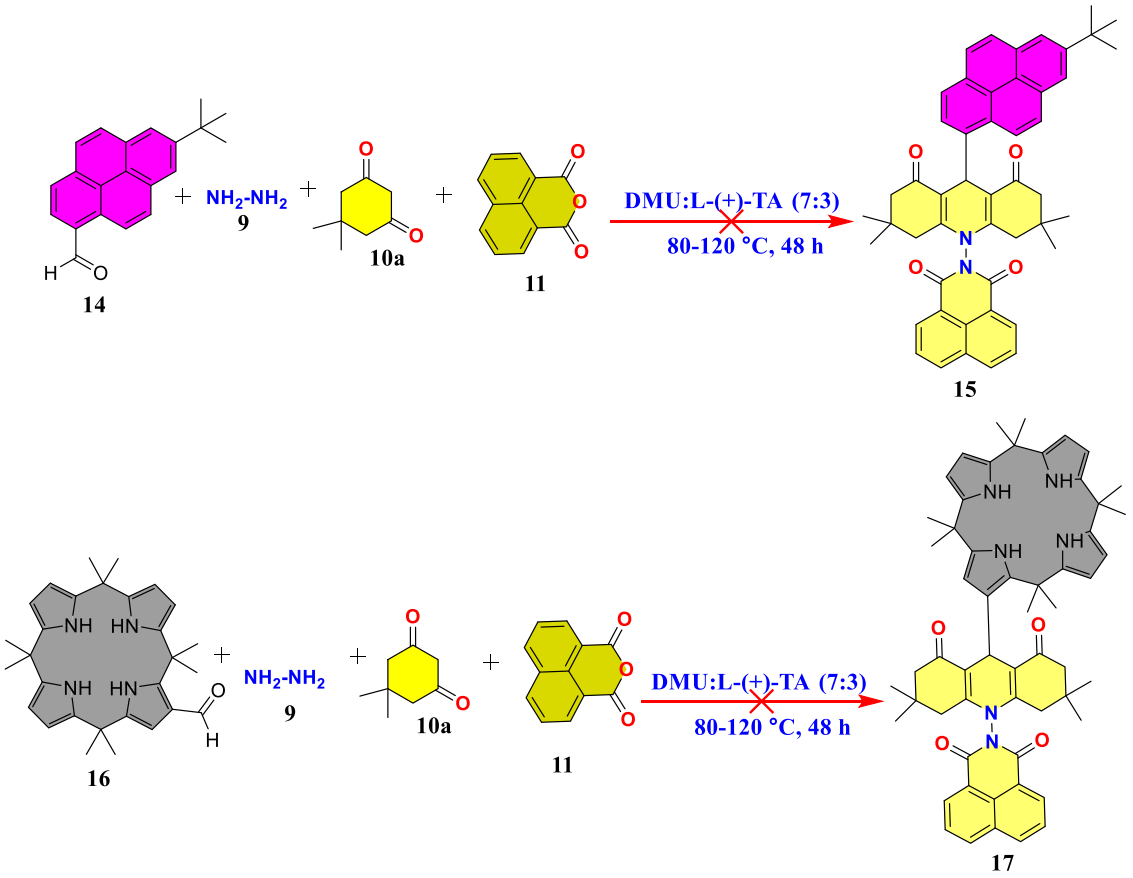
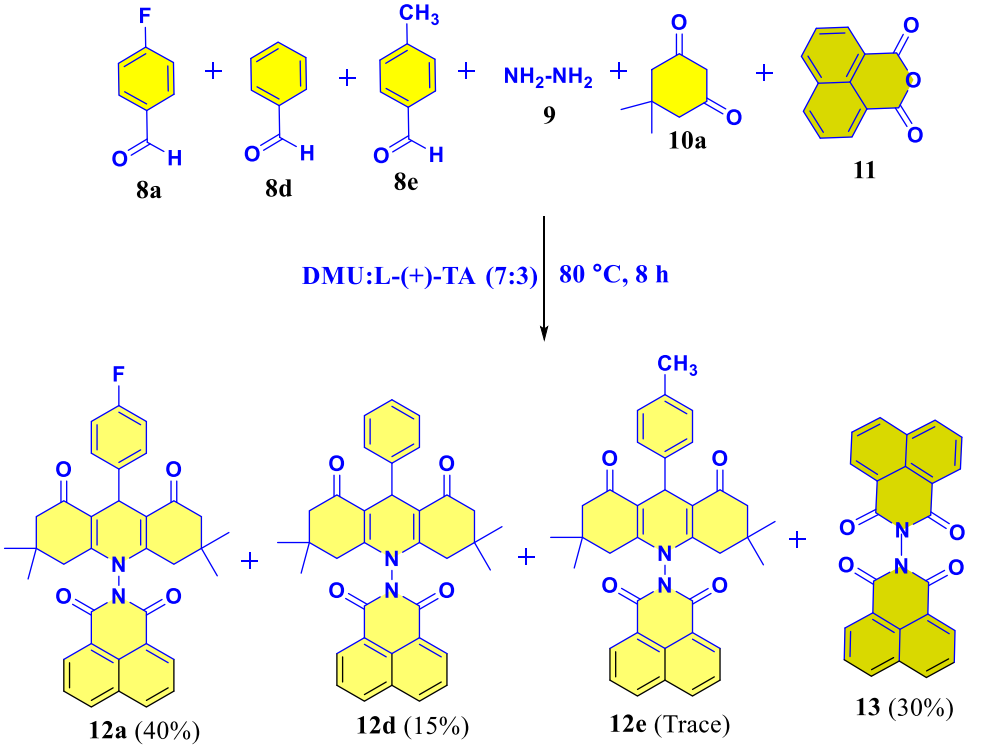
Scheme 2. Schematic Illustration of Unsuccessful Attempts to Synthesize Functionalized Naphthalimide−Acridine Conjugate Compounds (15 and 17) *via* DMU/TA (7:3)



Scheme 3. Competitive Reaction for the Preparation of Naphthalimide−Acridine Conjugates (12a, 12d, and 12e) Using DMU/TA (7:3)



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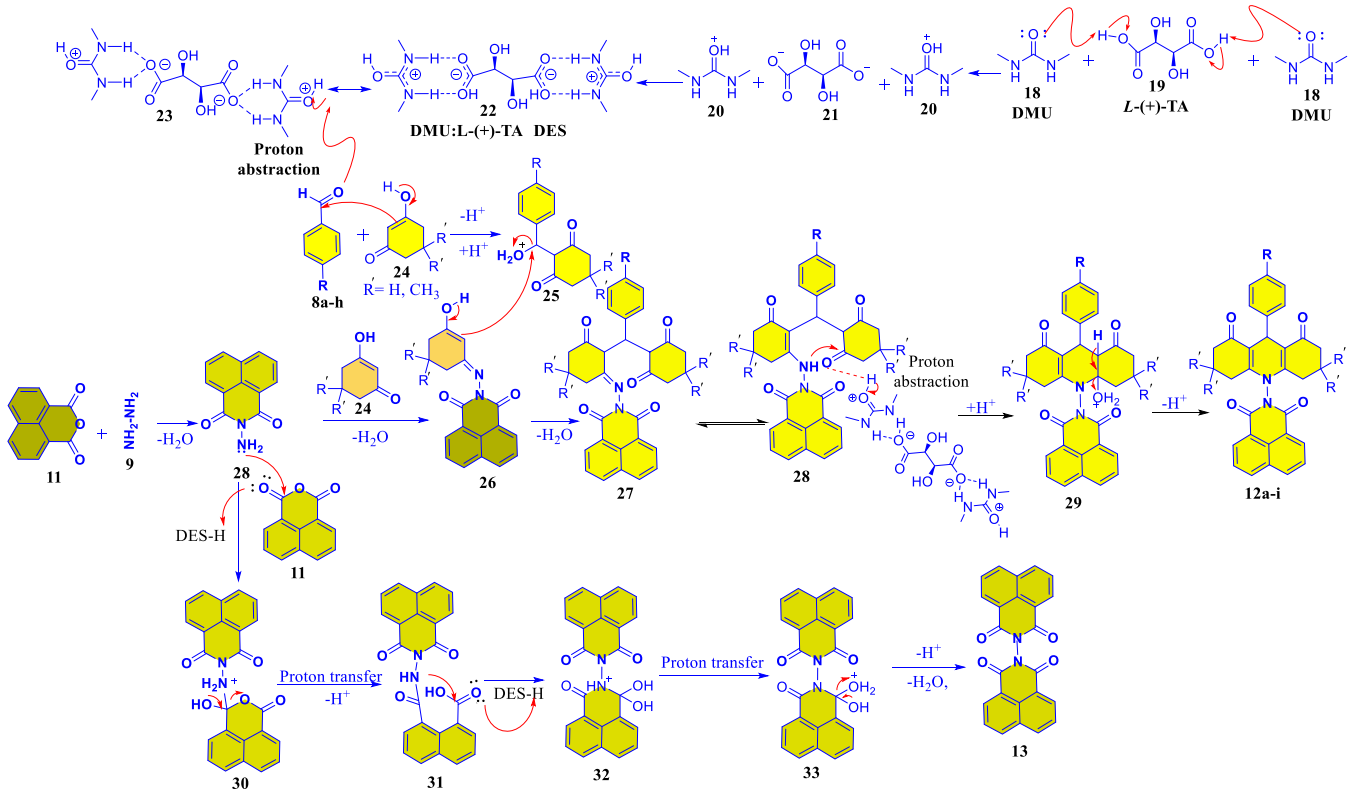
Scheme 4. Probable Mechanism for the Synthesis of Naphthalimide−Acridine-Based Conjugates (12a−i) and Undesired Product (13)



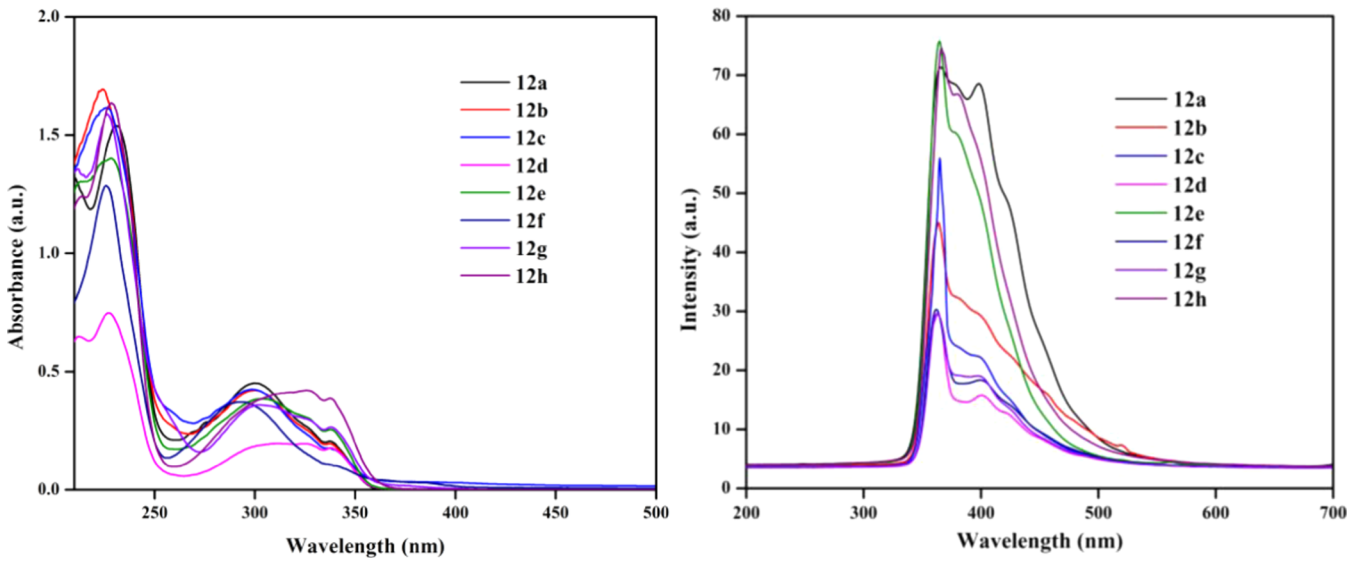


Figure 3. Absorption and emission spectra of 5 × 10^{-6} M solution of naphthalimide−acridine conjugates (**12a−h**) recorded at 25 °C in pure methanol.

less-intense bands between 290 and 327 nm along with shoulders, as depicted in Figure 3.

As far as the emission spectra of these compounds are concerned, they exhibit emission maxima at 364−367 nm, less-intense emission bands at 378−408 nm, and small shoulders at 421−520 nm (Figure 3). Interestingly, the fluoro conjugate compound (**12a**) exhibits an intense characteristic emission band at 366 nm, along with a slightly less-intense emission band at 399 nm and a shoulder at 423 nm. The precise values of fluorescence maxima for other conjugate compounds are as follows: **12b** (362 and 401 nm), **12c** (366 and 399 nm), **12d** (363 and 402 nm), **12e** (365 and 378 nm), **12f** (361 and 400 nm), **12g** (363 and 398 nm), and **12h** (367 and 381 nm).

CONCLUSIONS

In conclusion, various functionalized naphthalimide-based acridine-1,8-diones have fruitfully been synthesized *via* a one-pot multicomponent green approach exploiting the dual role of DMU/TA (7:3)-based eco-friendly reaction medium. The noticeable features of this particular green methodology are

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mild reaction conditions, great atom and step economy, involvement of an easy-to-use and inexpensive DES, good yields, no compulsion of an inert atmosphere, no usage of dangerous volatile organic solvents and/or corrosive catalysts, *etc*. The authors have the opinion that the recognized green protocol for naphthalimide-centered acridine-1,8-dione derivatives might be useful to assemble some other interesting bioactive molecules. The biological activities of these valued molecules are under consideration in collaboration with other groups within the country and will be published in due course.

EXPERIMENTAL SECTION

General Information. The compulsory chemicals and solvents were purchased from GLR innovations, Sigma Aldrich, SRL, Thermofisher, Alfa Aesar, Avra, Spectrochem, and TCI. The advancement of the reaction was examined by an analytical technique known as thin-layer chromatography (TLC) using an appropriate ratio of ethyl acetate and hexane for development. To purify the desired compounds, column chromatography with the aid of 100−200 mesh size silica gel was carried out using a proper mixture of ethyl acetate and hexane. All the known synthesized naphthalimide−acridine conjugate compounds (**12a−h** and **13**) were characterized by ^{1}H NMR spectra and the unknown synthesized naphthalimide−acridine conjugate compound (**12i**) was characterized by ^{1}H NMR,^{13}C NMR, and high-resolution mass spectrometry (HRMS) taken in DMSO-d_6 on a Bruker-based spectrometer (400 and 500 MHz). The melting points for all these known compounds were taken on manual melting point apparatus (Tanco).

General Synthetic Method for Functionalized Naphthalimide−Acridine Conjugate Compounds (12a−i). In a specific experiment, 3 g of DMU/TA (7:3) was heated at 70 °C to get a clear melting mixture. Subsequently, the temperature was increased to the optimal temperature (80 °C). At this particular temperature, aromatic aldehyde (1 mmol), dimedone/cyclohexan-1,3-dione (2 mmol), hydrazine hydrate (1 mmol), and 1,8-naphthanoic anhydride (1 mmol) were simultaneously added. Afterward, the reaction was stirred at 80 °C for 6−10 h. Once the reaction is completed, observed through diminution of all the reactants on the TLC, 10−20 mL of water was added to the hot reaction mixture. The resultant solid precipitate was filtered off *via* a sintered glass funnel and thoroughly washed with water. The solid reaction mixture was dried and later purified through column chromatography *via* a suitable ratio of hexane and ethyl acetate (10−20%) to offer functionalized naphthalimide−acridine conjugate compounds (**12a−i**). In those cases where no precipitation occurs on adding water, workup using ethyl acetate and water was done trailed by column chromatographic purification.

General Procedure for the Recyclability of the DMU/TA (7:3) Mixture. Subsequent to the end of a specific reaction carried out *via* 3 g of DMU/TA (7:3), 10−20 mL of water was added slowly to a warm reaction mixture. In most cases, this addition of water leads to precipitation of a product, which afterward was filtered using a sintered glass funnel. In typical cases, where no precipitation of the product occurs after water addition, liquid−liquid extraction *via* ethyl acetate and water was done. The aqueous phase comprising the DES in both the aforesaid cases was concentrated to get a solid DES, which afterward was dried and reprocessed in the next cycle directly. Similar practices were repeated.[48]

*Compound **12a**.* Pale-yellowish solid; mp 271−274 °C; yield 60%[1];H NMR (400 MHz, DMSO-d_6) δ 8.56−8.52 (m, 4H), 7.94−7.90 (m, 2H), 7.19−7.16 (m, 2H), 7.04 (t, J = 8.8 Hz, 2H), 4.50 (s, 1H), 2.54−2.05 (m, 8H), 1.03 (s, 6H), 0.89 (s, 6H). The ^{1}H NMR spectrum matched with the reported one.[17]

*Compound **12b**.* Pale-yellowish solid; mp 252−255 °C; yield 58%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56−8.51 (m, J = 11.3, 4H), 7.94−7.89 (m, 2H), 7.28−7.16 (m, 4H), 4.49 (s, 1H), 2.55−2.06 (m, 8H), 1.03 (s, 6H), 0.89 (s, 6H). The ^{1}H NMR spectrum matched with the reported one.[17]

*Compound **12c**.* Yellowish solid; mp 272−275 °C; yield 55%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56−8.53 (m, 4H), 7.94−7.91 (m, 2H), 7.42−7.11 (m, 4H), 4.47 (s, 1H), 2.55−2.06 (m, 8H), 1.03 (s, 6H), 0.89 (s, 6H). The ^{1}H NMR spectrum matched with the reported one.[17]

*Compound **12d**.* Light-yellowish solid; mp 272−275 °C; yield 52%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56−8.52 (m, 4H), 7.94−7.90 (m, 2H), 7.22−7.07 (m, 5H), 4.51 (s, 1H), 2.54−2.05 (m, 8H), 1.02 (s, 6H), 0.88 (s, 6H). The ^{1}H NMR spectrum matched with the reported one.[17]

*Compound **12e**.* White solid; mp 260−263 °C; yield 50%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56−8.53 (m, 4H), 7.94−7.91 (m, 2H), 7.04−6.99 (m, 4H), 4.46 (s, 1H), 2.54−2.04 (m, 11H), 1.02 (s, 6H), 0.88 (s, 6H). The spectral data are in accordance with the literature.[17]

*Compound **12f**.* Pale-yellowish solid, mp 267−270 °C; yield 49%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.57−8.53 (m, 4H), 7.94−7.90 (m, 2H), 7.07−6.75 (m, 4H), 4.45 (s, 1H), 3.67 (s, 3H), 2.53−2.04 (m, 8H), 1.02 (s, 6H), 0.89 (s, 6H). The ^{1}H NMR spectrum matched with the reported one.[17]

*Compound **12g**.* Creamy white solid; mp 265−267 °C; yield 48%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56−8.52 (m, 4H), 7.93−7.89 (m, 2H), 6.95−6.54 (m, 4H), 4.38 (s, 1H), 2.80 (s, 6H), 2.52−2.03 (m, 8H), 1.02 (s, 6H), 0.90 (s, 6H). The ^{1}H NMR spectrum matched with the reported one.[17]

*Compound **12h**.* White solid; mp 258−260 °C; yield 51%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.15 (s,1H), 8.56−8.52 (m, 4H), 7.93−7.90 (m, 2H), 6.94−6.56 (m, 4H), 4.40 (s, 1H), 2.52−2.04 (m, 8H), 1.02 (s, 6H), 0.89 (s, 6H). The ^{1}H NMR spectrum matched with the reported one.[17]

*Compound **12i**.* Creamy white solid; yield 56%; ^{1}H NMR (500 MHz, $CDCl_3$) δ δ 8.56 (d, J = 7.0 Hz, 2H), 8.16 (d, J = 8.0 Hz, 2H), 7.69−7.77(m, 2H), 7.17 (s, 2H), 6.82 (t, J = 8.5 Hz, 2H), 4.71 (s, 1H), 2.60−2.49 (m, 4H), 2.30−2.24 (m, 4H), 1.97−1.89 (m, 4H).^{13}C NMR (126 MHz, $CDCl_3$) δ 196.64, 164.08, 161.10, 140.31, 134.60, 135.98, 133.53, 131.66, 130.03, 129.96, 127.17, 122.45, 116.92, 115.06, 114.89, 37.06, 31.19, 27.27, 20.43. HRMS (ESI, Q-TOF) m/z calculated for $C_{31}H_{23}FN_2O_4$ $[M + H]^+$ = 507.1715, observed $[M + H]^+$ = 507.1720.

*Compound **13**.* Yellow solid; mp 204−207 °C; yield 30%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.50−8.44 (m, 8H), 7.87 (t, J = 7.5 Hz, 4H). The ^{1}H NMR spectrum matched with the reported one.[50]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c04026.

Recyclability test of DMU/TA (7:3) and copies of ^{1}H NMR, ^{13}C NMR, and HRMS spectra (PDF)

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Notes

The authors declare no competing financial interest.

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