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Original article

An efficient, sustainable approach to the chemo and regioselective synthesis of novel spiroindenoquinoxaline grafted piperidone hybrid heterocycles

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ABSTRACT

An efficient, eco-friendly and sustainable approach for the synthesis of novel spiroindeno[1,2-*b*]quinoxaline-3-phenylspiro[4,3″]benzylidenepiperidone ring system has been developed by a one-pot four component [3 + 2] cycloaddition strategy. The 1,3-dipole generated *in situ* from quinoxalinone and L-phenylalanine reacts with the highly functionalized dipolarophiles, bisarylidene piperidones affording spirohybrid heterocycles in good yields. The unexplored novel class of dispirohybrid heterocycles obtained possess three C—N and two C—C bonds with four adjacent stereogenic carbons, out of which two is spirocarbons. The structure of compounds was elucidated using ^{1}H, ^{13}C and mass spectroscopic studies.

1. Introduction

Exploring structurally intriguing hybrid heterocycles possessing important biological activities is a great challenge in organic and medicinal chemistry. Multicomponent 1,3-dipolar cycloaddition methodology is one of the efficient strategy for the construction of structurally complex architecture (Padwa, 2002; Karthikeyan et al., 2007) and holds prominent place in modern drug discovery research owing to their advantages such as avoiding isolation and purification of intermediates, improving atom economy, minimization of waste, selectivity and yield of product, formation of single product from three or more reactant in a single synthetic operation with multiple bond forming efficiency (Bortolini et al., 2007; Hong et al., 2007). These credentials make this strategy, economic and environmentally friendly. In this context, ionic liquids were widely accepted as green solvents due to their iconicity, stability, solvating properties, high thermal tolerance, acid and basic nature. In recent past years, many libraries of biologically significant spiroheterocyclic hybrids were synthesized via this green synthetic protocol using ionic liquids (Michael Rajesh et al., 2012; Arumugam et al., 2019)

Spiro compounds are attractive target in organic synthesis due to their exclusive three-dimensional structural nature that makes to interact more efficiently with binding pockets in designated enzyme of the biological system and have free solubility than planar aromatic ring system, a key property in the process of drug discovery. Among them, spiropyrrolidine is an important structural motif as its active moiety ubiquitous in several naturally occurring alkaloids (Trost and Brennan, 2009) and many other biologically potent synthetic compounds. For example, spirotryprostatin (Bhaskar et al., 2012), coerulescine (Reddy and Douglas, 2010), elecomine (Deppermann et al., 2010), pteropodine (Kang et al., 2002), horsfiline (Marti and Carreiram, 2003), formosanine (Singha et al., 2013), rychnophyilline, strychnofoline (Angenot, 1978), alstonisine (Garnick and Le Quesne, 1978), MI-219, M-219, MI-888. These compounds exhibited multifarious biological activities including potential antileukaemic (Abou-Gharbia and Doukas, 1979), anticonvulsant (Jiang et al., 2006), local anaesthetic (Kornett and Thio, 1976), antiviral (Lundahl et al., 1972), anticancer (Kathirvelan et al., 2015), antimycobacterial (Arun et al., 2014), anti-inflammatory, anti-microbial (Rajesh et al., 2011), cholinesterase inhibition activities (Kia et al., 2014), potent blocker of human NK-1 receptor (Kornett and Thio, 1976) and p53-mdm2 interaction (Skiles and Mc Neil, 1990).

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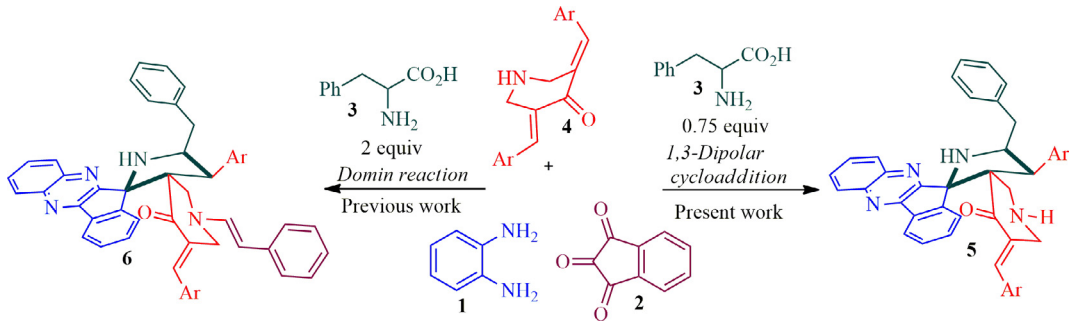


Scheme 1. Present and previous work.

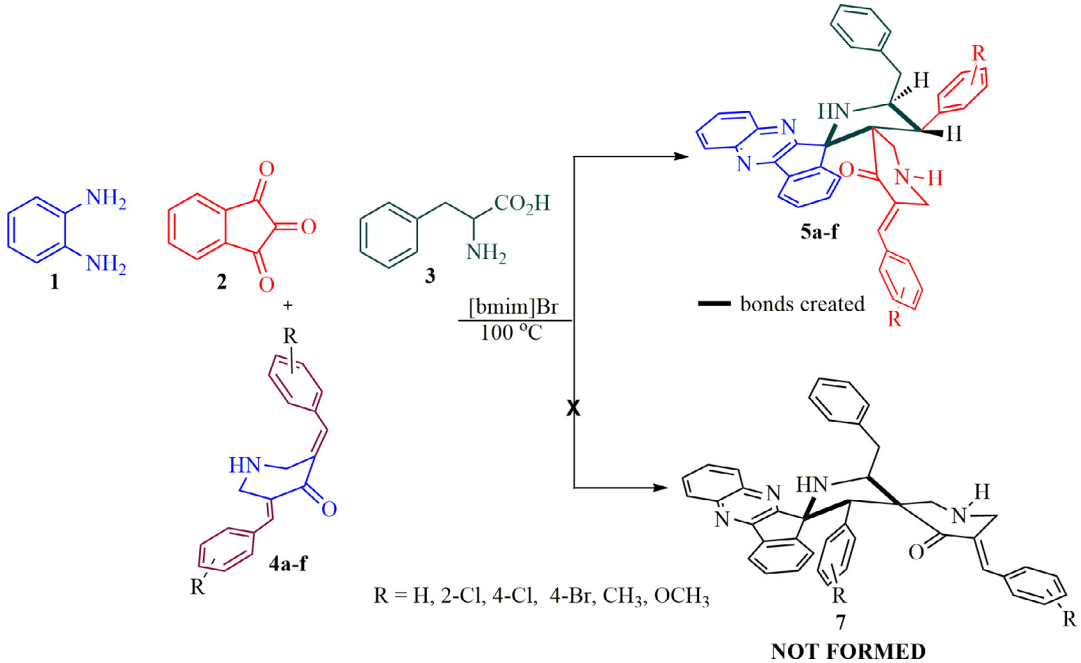
Piperidone is also an important class of heterocyclic entity, being a useful candidate for the synthesis of naturally occurring alkaloids. Piperidone fused heterocyclic compounds displayed interesting biological activities including herbicidal, bactericidal, fungicidal activities (Dimmock et al., 1994, 1992) and act as potent in vitro blocker for human placental aromatase (Barondi et al., 1996). Piperidin-3-one derivatives are used as potential synthon for the synthesis of antimalarial agents *viz*., febrifugine and isofebrifugine (Takeuchi et al., 2000). In particular, 3,5-bis(aryli dene)piperidin-4-ones showed potent cytotoxic, anticancer agents and are used as essential part for the synthesis of indolizidine alkaloids and tachykinin antagonists (Shintani et al., 2004; Lee et al., 2001). Furthermore, piperidin-4-one hydrochloride is an EPR active component, used as a spin trap in several EPR studies (Dzwigaj and Pezerart, 1995) and its hydrazine derivatives possess antioxidants properties. Besides, piperidin-2-one embedded heterocycles were also used as chiral intermediates in the synthesis of several synthetic and natural compounds with significant biological activities *viz*., anticancer (Fleet et al., 1989), anti-HIV (Winkler and Holan, 1989) and glycosidase inhibition activities (Fleet et al., 1988). On the other hand, quinoxaline is an active moiety in brimonidine and varenicline drugs which are potent drug candidate for the treatment of glaucoma (Danylkova et al., 2007) and smoking cessation therapy (Mohanasundaram et al., 2008). Besides, quinoxaline analogs act as in vitro Pim-3 kinase inhibitors (Gavara et al., 2010) and potent 5-HT3 receptor agonist (Campiani et al., 1999).

The aforementioned biological significance of spiropyrrolidine, piperidone and quinoxaline sub-structures in conjunction with our interest in the preparation of new class of hybrid heterocycles employing multicomponent 1,3-dipolar cycloaddition strategy, led us now to report the synthesis of hybrid heterocycles incorporating piperidone and spiro-pyrrolidinyl-indenoquinoxaline sub units. In the present work, the relatively less explored non-stabilized 1,3-dipole component derived from L-phenylalanine and indenoquinoxaline *via* decarboxylative condensation reaction has been employed. The synthetic strategy of the present and previous work has been described in Scheme 1.

2. Materials and methods

2.1. Synthesis of spiropyrrolo-indenoquinoxaline tethered piperidone heterocyclic hybrids, *5a-f*

A mixture of ninhydrin (1 mmol), 1,2-aryldiamine (1 mmol) and 1-butyl-3-methylimidazolium bromide [bmim]br (200 mg) were heated with stirring at 100 °C for 10 min. Then 2-amino-3-phenylpropanoic acid (0.75 mmol) and piperidone derivative



Scheme 2. Synthesis of dispiroindenoquioxaline tethered piperidone hybrid heterocycles, **5.**

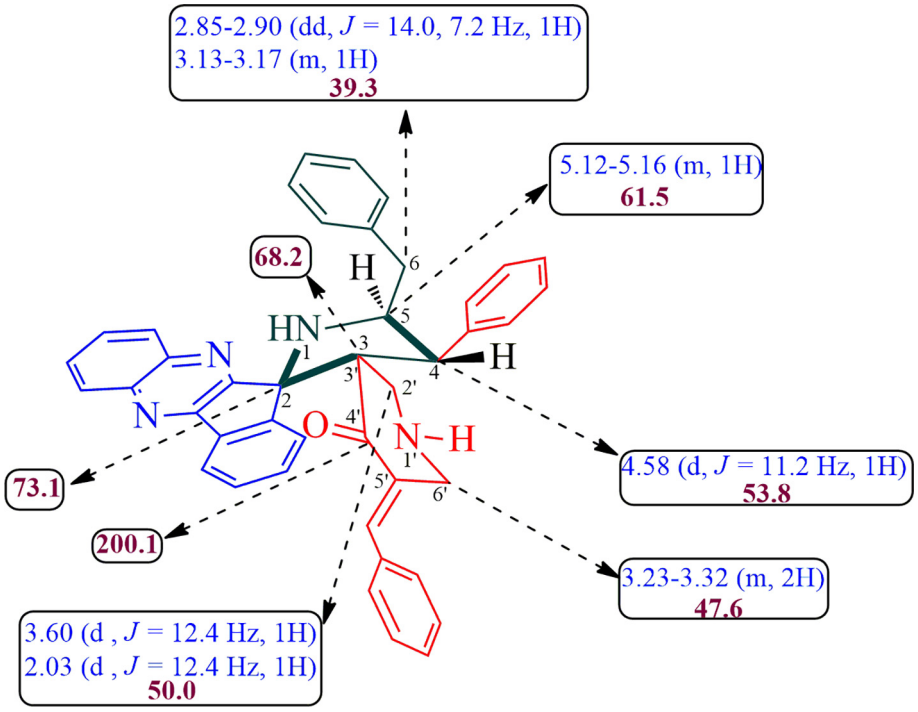


Fig. 1. Selected chemical shift of **5a.**

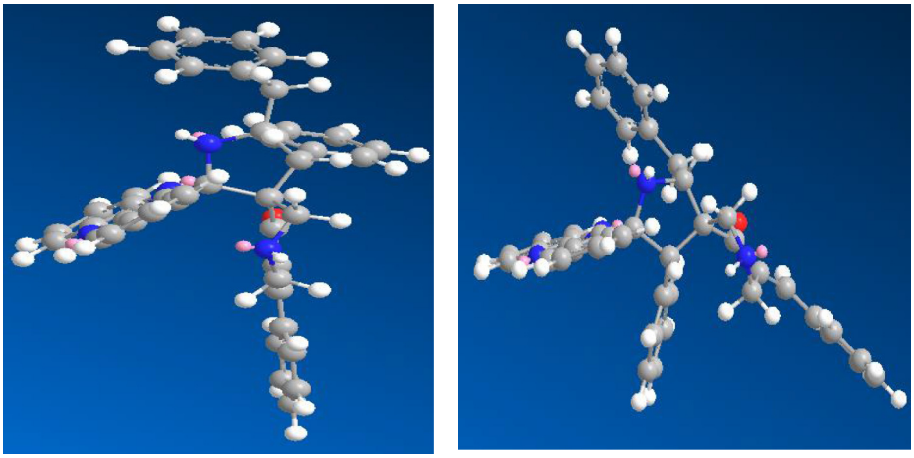
(1 mmol) was added to the reaction mixture and stirred further for 50 min at same temperature. After completion of the reaction as evidenced by thin layer chromatography (TLC), EtOAc (2 × 5 mL) was added to the reaction mixture and stirred for 10 min. The organic phase was extracted and the excess EtOAc was removed under vaccum, the residue obtained was purified by column chromatography using hexane: ethyl acetate (3:7 v/v) as eluent to afford pure products **5** in good yield.

2.2. 5-Benzyl-4-phenyl-spiro[2.3′]indenoquinoxalino-spiro[3.3′′]-5′′benzylidenepiperidone-pyrrolidine, ***5a***

White color solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm 2.03 (d, J = 12.4 Hz, 1H), 2.85–2.90 (dd, J = 14.0, 7.2 Hz, 1H), 3.13–3.17 (m, 1H), 3.23–3.32 (m, 2H), 3.60 (d, J = 12.4 Hz, 1H), 4.58 (d, J = 11.2 Hz, 1H), 5.12–5.16 (m, 1H), 6.83–6.85 (m, 3H, ArH), 7.16–7.29 (m, 9H, ArH), 7.34–7.40 (m, 4H, ArH), 7.46–7.50 (m, 1H), 7.59–7.67 (m, 4H, ArH), 7.92 (d, J = 7.2 Hz, 1H), 8.00–8.02 (m, 1H), 8.14–8.16 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): 39.3, 47.6, 50.0, 53.8, 61.5, 68.2, 73.1, 121.7, 121.8, 126.2, 126.9, 127.2, 128.1, 128.3, 128.4, 128.9, 129.0, 129.3, 129.7, 131.0, 134.7, 135.0, 136.6, 137.3, 138.2, 138.6, 140.6, 141.6, 148.4, 154.9, 166.2, 200.1; LC/MS(ESI): m/z = 611 (M^+); Anal. Calcd for $C_{42}H_{34}N_4O$: C, 82.60; H, 5.61; N, 9.17%; Found C, 82.71; H, 5.69; N, 9.24%.

3. Results and discussion

Recently, we have synthesized a small library of structurally unusual *N*-stryrylpiperidone tethered dispiropyrrolidine hybrid



Product **5a**; Total Energy: 48.7470 kcal/mol

Other possible product:**7**; Total Energy: 55.1475 kcal/mol

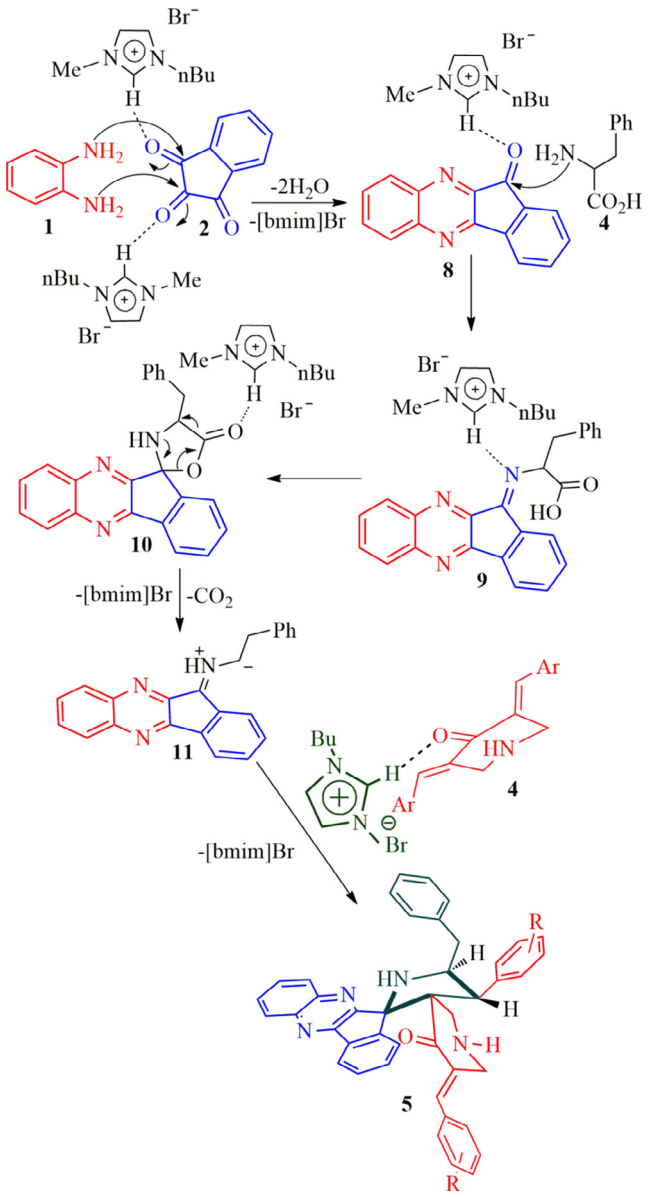
Fig. 2. Energy mimization diagram of compound **5** and other possible regioisomer **7.**

heterocycles **6** in good yields employing four component 1,3-dipolar cycloaddition cascade protocol (Almansour et al., 2019). Firstly, the cascade reaction sequence was carried out with an equimolar amount of 1,2-phenylenediamine **1**, ninhydrin **2**, L-phenylalanine **3** and arylidenepiperidone **4** under reflux in methanol, affording inseparable mixture of products on TLC analysis. Hence, the same reaction was attempted with different ratio of amino acid **3** (1 mmol to 1.75 mmol) and did not get fruitful results. The unusual *N*-styryl dispiropyrroldine hybrids **6** was obtained in moderate yield when two mole equivalents of amino acid **3** was employed. However, the reaction was optimized under the various solvent conditions including ionic liquids and product **6** was obtained in good yields in ionic liquids when compared to the other organic solvents. The present work describes the synthesis of dispiropyrrolidine tethered piperidone hybrid heterocycles **5**. The previous reaction conditions and ratio of reactant as mentioned above kept in mind, the reaction was further investigated to get the desired product **5** instead of **6**. In this context, the present work was performed with benzylidenepiperidone **4** (1 mmol) and non-stabilized 1,3-dipole component derived from quinoxalinone (1 mmol) and L-phenylalanine (0.5 mmol) under reflux in methanol, delightfully the expected dispiropyrrolidine hybrid heterocycles **5** afforded in moderate yield (Scheme 2). However, the starting substrate was not diminished even after prolonged reaction time. Further, the same four component reaction was attempted with 0.6 mmol equivalent of amino acid **3** and the product was obtained in a better yield. But the starting substrates were not completely disappeared even after several hours. Finally, the reaction was carried out with 0.75 mmol equivalent of L-phenylalanine and observed a substantial improvement in yield of product (55%). The four-component reaction was further investigated to improve the yield of product **5**, in this direction the reaction was performed with 0.8–0.9 mmol equivalent of amino acid **3**, the reaction leads to the formation of product **6** with inseparable mixture of the byproduct as evidenced by TLC analysis. As an alternative, the reaction was carried out with ionic liquid, [bmim]Br (Arumugam et al., 2019) and the product furnished in good yield. Thus, a mixture of *o*-phenylenediamine **1** (1 mmol), ninhydrin **2** (1 mmol), L-phenylalanine **3** (0.75 mmol) and dipolarophile **4** (1 mmol) were heated with constant stirring under [bmim]Br at 100 °C and the reaction progress has been monitored after every 10 min interval. After completion of the reaction, the mixture was diluted with ethyl acetate. The collected organic layer was removed under reduced pressure, the desired product **5** (65%) was obtained in good yields. The structurally complex dispiropyrrolidine hybrid heterocycles possess four adjacent stereocenters, out of which two are spirocarbons. In addition, the complex heterocycles possess two C—C bonds and three C—N bonds.

The structure of all dispiropyrrolidine tethered piperidone hybrid heterocycles was characterized by ^{1}H, ^{13}C, mass spectroscopic and elemental analysis (Fig. 1). As a representative case, the structural assignment of **5a** is described below. In its ^{1}H NMR spectrum, the benzylic hydrogen (H-4) was assigned at δ 4.58 (J = 11.2 Hz) as doublet. The multiplet at δ 5.12–5.16 ppm was assigned to H-5 hydrogen of pyrrolidine ring. The doublet of doublets at δ 2.85–2.90 ppm and a multiplet at δ 3.13–3.17 were assignable to H-6 hydrogens. The two doublets at δ 3.60 and δ 2.03 ppm (J = 12.4 Hz) were belongs to piperidone H-2″ hydrogens and a multiplet at δ 3.23–3.32 ppm were assigned to H-6″ hydrogens of piperidone ring. All aromatic ring hydrogen appeared as multiplets from 6.83 to 8.16 ppm. The H-4 (J = 11.2 Hz) and H-5 hydrogens are *trans* to each other as evidenced by their coupling constant value. In its ^{13}C NMR spectrum, the quinoxaline attached to pyrrolidine ring spirocarbon (C-2) resonated at δ 73.1 ppm and a signal at δ 68.2 ppm was assigned to piperidone ring attached spirocarbon (C-3″). The signals at 53.8 ppm and 61.5 ppm were assigned to C-4 and C-5 of pyrrolidine ring carbon, respectively. Similarly, the signals at δ 47.6 and δ 50.0 ppm were due to the C-2″ and C-6″ carbons of piperidone ring. The piperidone carbonyl carbon exhibited at δ 200.1 ppm. The structure of compound **5a** was further confirmed by mass spectroscopic analysis.

The other possible regioisomeric spiroheterocyclic hybrid **7** was not observed even in traces due to the possible secondary orbital interaction between 1,3-dipole component **11** and α, β-unsaturated exocyclic ketone of dipolarophile **4**. In addition, the electron rich 1,3-dipole component **11** preferentially attacks electron deficient β-carbon of α, β-unsaturated dipolarophile to afford regioisomeric product **5**. Further, we proved the formation of spiroheterocyclic hybrid **5** through computational investigation using energy minimization calculation (mm2) and found that compound **5** has lower energy 48.7470 kcal/mol when compared to other possible regioisomer **7** with higher energy 55.1475 kcal/mol, revealing that compound **5** is more stable than **7** as illustrated in Fig. 2

The four-component reaction presumably takes place *via* 1,3-dipolar cycloaddition sequence and reasonable mechanism for



Scheme 3. Plausible mechanism for the formation of dispiroindenoquinoxaline tethered piperidone heterocyclic hybrids, **5.**

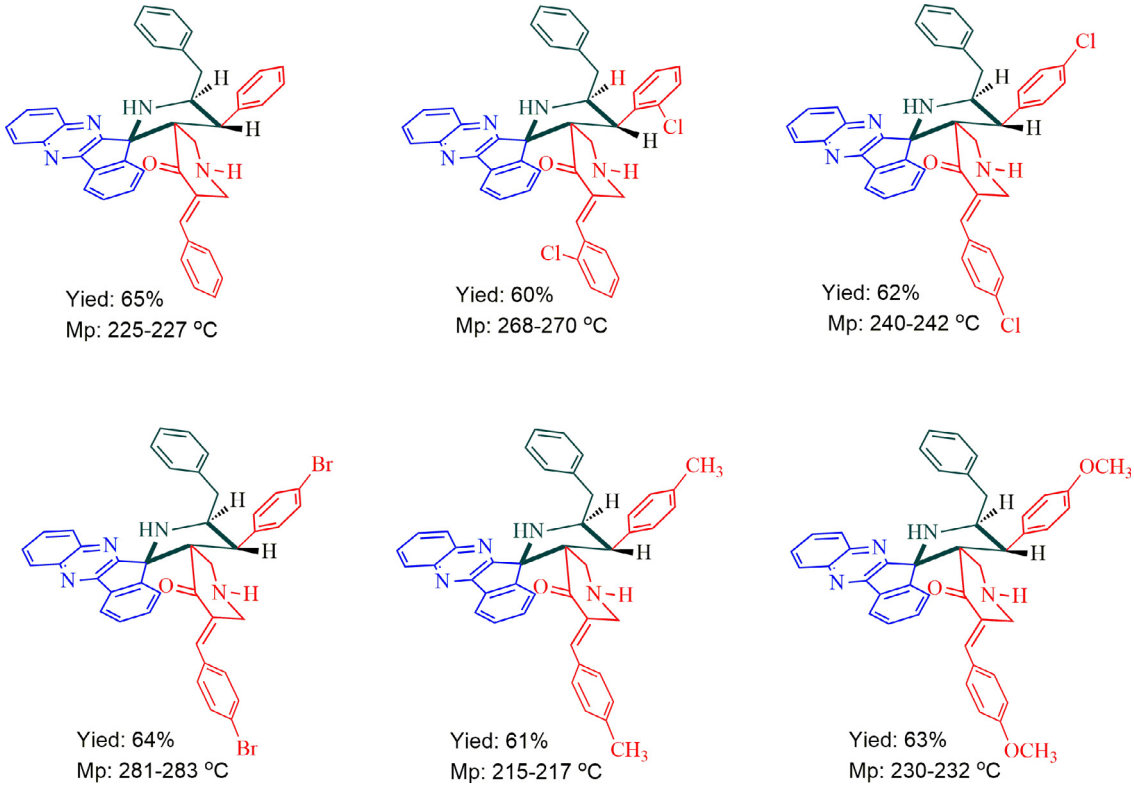


Fig. 3. Synthesis of spiropyrrolidine-indenoquioxaline-piperidone hybrids heterocycles, **5a-f.**

the construction of hybrid heterocycles **5a-f** is demonstrated in Scheme 3. Initially, aryldiamine **1** and indene-1,2,3-trione **2** reacts with indeno[3,2-*b*]quinoxalin-11-one **7** with spontaneous elimination of two equivalents of H_2O molecules. The indeno[3,2-*b*] quinoxalin-11-one intermediate **8** reacts with 2-amino-3-phenylpropanoic acid **4** to form spiro-oxazolidinone intermediate **10** *via* iminium component **9.** The spiro-oxazolidinone **10** generates the highly reactive 1,3-dipole **11** *via* decarboxylative condensation**.** Simultaneously, the non-stabilized 1,3-dipole component of ylide **11** attacks one of the C═C bond of the electron deficient dipolarophile **4** by chemo and regioselectively furnishing the target heterocyclic hybrid **5**. It is pertinent to note that ionic liquid, [bmim]Br play a vital role in the cycloaddition reaction sequence both as catalyst and solvent as described in Scheme 3. The electron deficient hydrogen of [bmim]br interact with the carbonyl unit of indene-1,2,3-trione **2**, quinoxalinone **8**, spiro-oxazolidinone **10** includes iminium intermediate **8** to form hydrogen bond that would increase the electrophilicity of the all components which further accelerated the nucleophilic attack of (i) *o*-phenylenediamine (ii) 2-amino-3-phenylpropanoic acid and (iii) formation of azomethine ylide *via* spiro-oxazolidinone intermediate (iv) formation of product *via* 1,3-dipole component and electron deficient dipolarophile (see Fig. 3).

4. Conclusion

Hybrid heterocycles comprising spiroindenoquinoxaline, pyrrolidine and piperidone has been synthesized in good yields employing [bmim]Br assisted one pot four component [3 + 2] cycloaddition strategy. A relatively less explored non-stabilized 1,3-dipole component, the azomethine ylide derived from quinoxalinone and L-phenylalanine via decarboxylative condensation has been used. The formation of cycloadduct via two C—C and three C—N bonds in single synthetic transformation which possess four adjacent stereocenter, out of which two are spirocarbons. Further, the biological evaluation of these compounds will be published in due course.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jksus.2020.08.013.

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