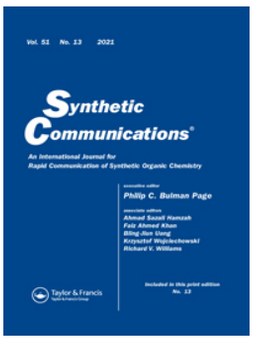

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A sequential multicomponent reaction (SMCR) strategy: Synthesis of novel pyrazolo-1,4-dioxaspiro[4,5]decane grafted spiro-indenoquinoxaline pyrrolidine heterocycles

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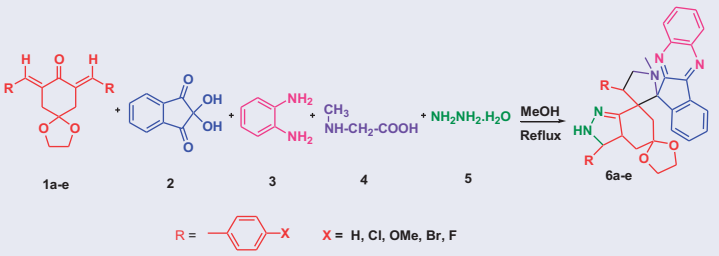
ABSTRACT

A facile and expedient one-pot sequential five-component synthesis of highly substituted trispiro-pyrrolidine heterocycles is described. The key step involves [3 + 2]-cycloaddition of azomethine ylide. This multicomponent reaction (MCR) strategy provides a mild reaction condition, high yield of the products, high regioselectivity, and operational simplicity to assemble complex structural entity in a single operation. The structure of product was confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, and high-resolution mass spectroscopic analysis. A theoretical insight is provided through MM2 calculation for the formation of the observed products.

GRAPHICAL ABSTRACT



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Azomethine ylide; pyrazolo-1,4-dioxa-spiro[4,5]decane; indenoquinoxaline; multi-component reaction (MCR); spiro-pyrrolidines

Introduction

A multicomponent reaction (MCR) can be simply classified as a reaction in which three or more components are combined together in a single reaction vessel to produce a final product or products displaying features of all inputs and thus offer greater possibilities for molecular diversity per step with a minimum of synthetic time and effort. Multicomponent reactions offer a convenient strategy for the rapid elegant and convergent construction of complex and structurally diverse organic molecules in a single operation resulting in substantial minimization of waste, labor, time, and cost[1,2] and play a vital role in combinatorial and diversity-oriented synthesis.[3] MCRs result in high atom and step economy. MCRs are more advantageous than conventional approach which

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generally involves the use of multistep reaction sequence which is typically associated with low yields, high cost, tedious isolation, and purification of the resulting products. One of the major challenges often encountered in modern drug discovery program is the design of highly efficient chemical reactions for accessing structurally complex and diverse compounds, possessing important biological activities, in a minimum number of synthetic steps. MCR strategy can be useful in this regard which has emerged as an advanced tool for sustainable organic synthesis. Among MCRs, the intermolecular [3 + 2]-cycloaddition of azomethine ylides to olefinic dipolarophiles[4] constitutes a facile approach for the efficient assembly of five-membered heterocyclic rings of biological importance particularly pyrrolidines and spiro-pyrrolidines due to their occurrence in a large number of natural products.[5] Spiropyrrolidines act as potential antileukemic,[6] anticonvulsant[7] antiviral,[8] local anesthetic,[9] and anti-inflammatory agents.[10] Quinoxalines, indazoles, and pyrazoles are important classes of nitrogen-containing heterocycles with broad spectrum of biological activities such as anti-viral,[11] anti-cancer,[12] anti-inflammatory,[13] anti-tubercular,[14] anti-leishmanial,[15] anti-malarial,[16] and anti-depressant activities.[17] Recently, some of the quinoxaline derivatives such as brimonidine and varenicline have been approved by the food and drug administration for the treatment of glaucoma[18] and anti-smoking therapy.[19] Some of the synthetic and naturally occurring biologically significant spiro-pyrrolidine, quinoxaline, pyrazole, and dioxalane derivatives are shown (Fig. 1). The potential pharmaceutical significance of these backbones has led to a demand for the synthesis of hybrid systems incorporating all these significant entities in a single molecule.

Results and discussion

In continuation of our research in the area of cycloaddition reactions and with renewed interest in such complex spiro-pyrrolidine heterocycles,[20,21] we herein report for the first time, a mild, rapid, and a facile one-pot sequential five-component synthesis of highly substituted trispiroheterocyles containing 1,4-dioxa-spiro[4,5]decane, pyrrolidine, indenoquinoxaline, and pyrazole moieties using various unusual 7, 9-bis-[(*E*)-arylmethylidene]-1.4-dioxa-spiro[4,5]-decan-8-one derivatives, 1,2-phenylenediamine, ninhydrin, sarcosine, and hydrazine hydrate (Scheme 1).

The one-pot sequential five-component reaction involving ninhydrin **2**, 1,2-phenylenediammine **3**, sarcosine **4,** dipolarophile **1a,** and hydrazine hydrate **5** proceeded at reflux temperature in methanol, to give pyrazolo-1,4-dioxa-spiro[4,5]decane grafted spiro-indenoquinoxaline pyrrolidine **6a**. The multistep sequence of events involves, initial heterocyclization of phenylenediamine **3** with ninhydrin **2** giving indenoquinoxaline-11-one **7**[22] which further condensed with sarcosine **4** to produce 1,3-dipole, azomethine ylide **10** *via* thermal decarboxylation of **9**.[20a,b,23] The azomethine ylide **10** undergoes cycloaddition across one of the exocyclic double bond of the dipolarophile **1a** to afford the intermediate product **11** which undergoes cyclization with hydrazine to give the final product **6a** in good yield (Scheme 2).

Thus, the IR spectrum of 1-*N*-methyl-spiro[7.3′′]-3,3a,4,5,6,7-hexahydro-2H-indazole-3-(*p*-methoxyphenyl)–spiro-[5.2′]-1′,3′-dioxalane-spiro[2′′.11′′′]-indeno-[1,2-b]-quinoxaline-4-(*p*-methoxyphenyl)-pyrrolidine **6a** revealed the complete disappearance of carbonyl group

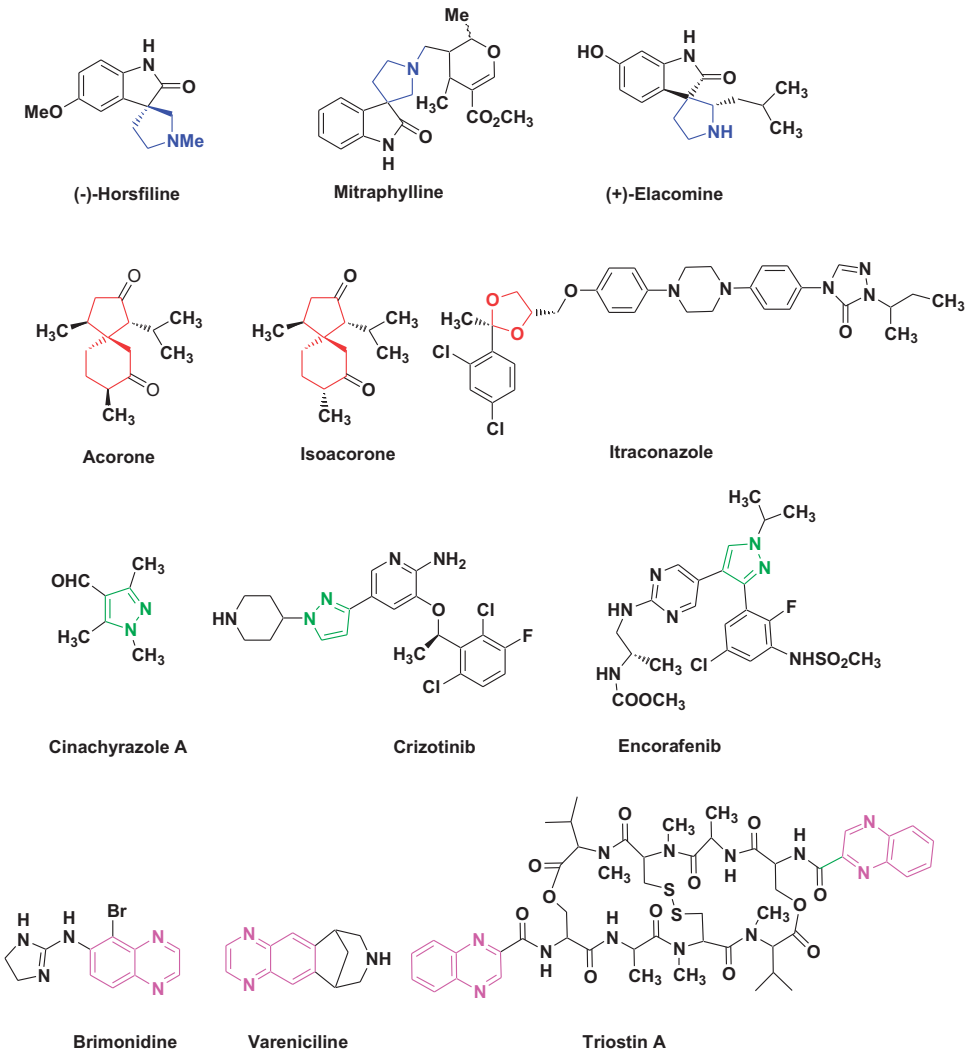
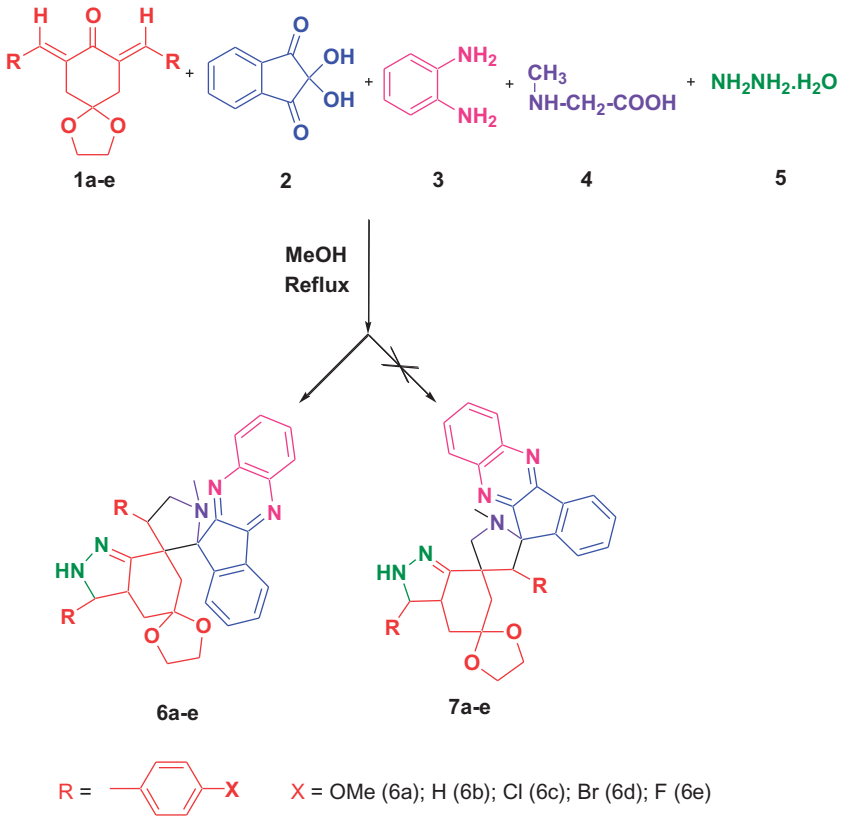


Figure 1. Some synthetic and naturally occurring biologically significant molecules having spiro-pyrrolidine, spiro[4,5]decane, dioxalane, pyrazole, and quinoxaline moieties.

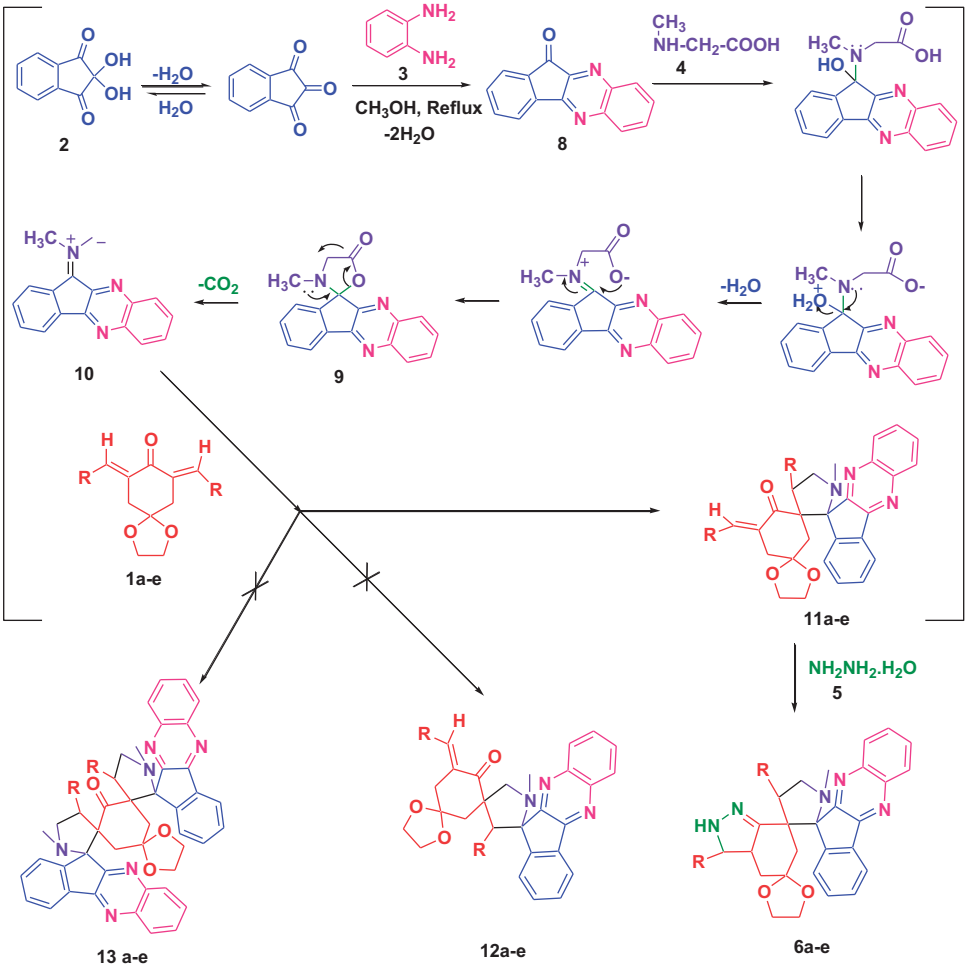
of cyclohexanone and exhibited a peak at 1605 and 3317 cm^{-1}due to the C = N and NH group of the pyrazole ring. The ^{1}H NMR spectrum of the product **6a** exhibited a singlet at δ 1.77 ppm due to -NCH_3 pyrrolidine protons. The two pyrrolidine-NCH_2 protons exhibited triplets at δ 3.55 and δ 4.14. The pyrrolidine ring proton attached to the aryl moiety exhibited a doublet of doublet at δ 5.14 ppm. The two methoxy groups on the aryl moiety exhibited a singlet at δ 3.79 and 3.84. The pyrazole ring proton attached to the aryl moiety exhibited a doublet at δ 4.28. The -CH ring proton fused to the pyrazole moiety exhibited a multiplet in the region δ 2.04 – 2.10. The -NH ring proton exhibited a singlet at 6.02 ppm. The aromatic rings protons exhibited a doublet at δ 6.84, δ 6.95, δ 7.84, triplet at δ 7.26, δ 7.49, δ 8.09 and multiplet in the region δ 7.61-7.74 and δ 8.22-8.26. No trace of the other regioisomer **7a** was observed. If the other regioisomer **7a** had been formed, the benzylic proton attached to the pyrrolidine ring would have appeared as a



Scheme 1. Synthesis of pyrazolo-1,4-dioxa-spiro[4,5]decane grafted spiro-indenoquinoxaline pyrrolidines **6a–e.**

singlet in the ^{1}H NMR spectrum of **7a** and this was not observed (Scheme 1). The off-resonance proton decoupled ^{13}C spectrum of **6a** exhibited peaks at 34.63 and 39.04 ppm due to the pyrrolidine NCH_3 and NCH_2 carbons.[21a] The two methoxy carbon resonated at 55.31 and 55.46 ppm. The two spirocarbon resonated at 73.26 and 78.18 ppm. The spiro carbon of the dioxalane ring resonated at 108.33 ppm (Table 1).[24] The C = NH carbon of the indazole ring resonated at 155.92 ppm and the signals of all other carbons appeared at appropriate chemical shifts in agreement with the proposed structure. The formation of the product is confirmed by mass spectral and elemental analysis. The high-resolution mass spectrum of **6a** showed a molecular ion peak (M^+) at 665.7738. The regiochemical outcome of the cycloaddition is also confirmed by the ^{1}H-NMR and single-crystal analysis of one of the similar intermediate in the isatin series [24] (Fig. S5, Supplementary file).

Even with an excess of 1,3-dipole (generated from excess of ninhydrin **2**, 1,2-phenylenediamine **3**, sarcosine **4**) and prolonged reaction times as evidenced by thin-layer chromatography (TLC), the reaction failed to proceed to give the bis-adduct **13a** (Scheme 2). Thus, the addition occurs at only one of the exocyclic double bonds. This may be due to the steric hinderance of the spiro-indenoquinoxaline pyrrolidine ring which prevents the attack of 1,3-dipole on the other exocyclic double bond. The formation of bis-adduct **13a** was ruled out from the high-resolution mass spectrum analysis.



Scheme 2. Mechanism for the formation of the product **6a–e** from azomethine ylide **10** and dipolarophile **1a–c** followed by annulation with hydrazine hydrate **5.**

Table 1. ^{13}C NMR values of spiro carbons.

S. no	C_2 pyrrolidine ring	C_3 pyrrolidine ring	Dioxalane ring
6a	73.26	78.18	108.33
6b	72.81	78.09	107.79
6c	72.84	78.12	108.00
6d	72.56	78.16	107.34
6e	72.44	78.12	108.20

In order to optimize and improve the yield of the product, the reaction was also carried out in various other solvents (Table 2). The results showed that even under refluxing condition for prolonged time in toluene (12 h), there was not much significant increase in the isolated yield of product (23%). However, in refluxing methanol, better chemical yield of the product was obtained (reaction time: 3.6 h.; isolated chemical yield: 79%) due to the better solubility of all the reactants favoring the easy formation of azomethine ylide **10.** Hence, methanol was chosen as solvent for invariably conducting the one-pot sequential MCR with various other dipolarophiles (**1b–e**), ninhydrin **2**,

Table 2. Optimization of solvent effect on the model reaction involving dipolarophiles **1a**, 1,2-phenylenediamine **2**, ninhydrin **3**, sarcosine **4,** and hydrazine hydrate **5**.

Entry	Solvent	Time (h)	Yield [b] (%)
1	Toluene [c]	12	23
2	1,4-dioxane	6.0	60
3	Tetrahydrofuran	6.0	54
4	Acetonitrile	3.3	66
5	Ethanol	3.8	73
6	Methanol	3.6	79

(a) Reaction condition: **1a**, 2, 3, 4, 5 (1 mmol) in solvent (20 mL) at reflux temperature; T(h): Time in hours, (b)Yield of the isolated product in percentage, (c) The reaction was carried out using a Dean–Stark apparatus.

Table 3. One-pot sequential five-component reaction of dipolarophiles **1a–e**, 1,2-phenylenediamine **2**, ninhydrin **3**, sarcosine **4,** and hydrazine hydrate **5**.

Entry	R	Methanol T (h)	Reflux Y (%)	Melting point (°C)
6a	OMe	3.6	79	197–200
6b	H	3.4	83	188–190
6c	Cl	3.3	86	166–167
6d	Br	3.5	84	158–159
6e	F	3.0	88	174–175

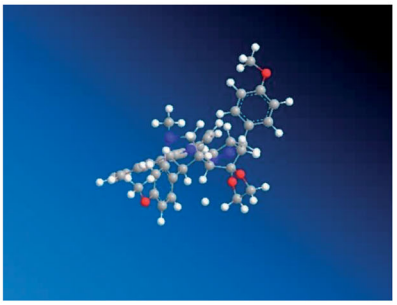
T(h): time in hours, Y (%): yield of the product in percentage

1,2-phenylenediamine **3**, sarcosine **4,** and hydrazine hydrate **5** affording pyrazolo-1,4-dioxa-spiro[4,5]decane grafted spiro-indenoquinoxaline pyrrolidines (**6b–e**) in good yield (Table 3).

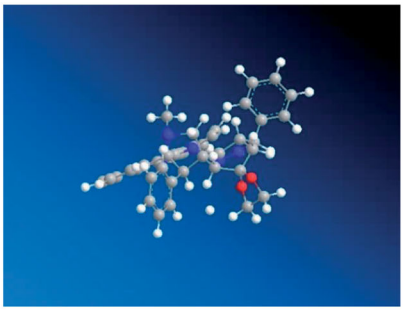
A sequential one-pot five-component is implemented in order to have the pyrazolo-1,4-dioxa-spiro[4,5]decane and indenoquinoxaline moiety on the pyrrolidine platform. When all the five components were added in one-pot and refluxed in methanol, mixture of unidentified inseparable products was obtained. Alternatively, when changes in the sequential addition were brought by the addition of hydrazine hydrate **5** with the dipolarophile **1a** followed by the addition of ninhydrin **2** and 1,2-phenylenediammine **3**, the product **6a** was formed in poor yield (20%). Hence, this methodology was abandoned.

Molecular mechanics (MM2)

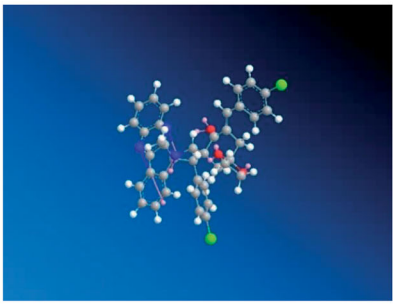
Molecular mechanics or force-field method use classical type models to predict the energy of a molecule as a function of its conformation. This allows predictions of equilibrium geometries and transition states and also relative energies between conformers or between different molecules. Molecular mechanics can be used to supply the potential energy for molecular dynamics computations on large molecules. In our study, molecular mechanics (MM2) calculations have been carried out to rationalize the formation of the spiroheterocyclic hybrid **6a–e**.[25,26] The energy minimized structure is expressed in kcal/mol. Through the MM2 calculations, it is observed that the total energy of the product **6a–e** formed, ranges from 63 to 81 kcal/mole (Fig. 2). Depending upon the various substituents on the hybrid heterocycle, the total energy of the individual product is different. The total energy of the possible regioisomer **12a–e** ranges from 74 to 90 kcal/mole (Fig. 3) whereas the total energy of the bis-cycloadduct **13a–e** ranges from 1010 to 1190 kcal/mole which is extremely large (Fig. 4). From the overall comparison of the total energy of the product formed **6a–e**, its possible regioisomer **12a–e**



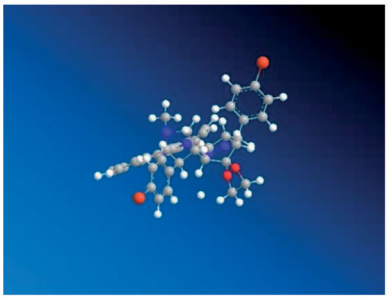
6a: Total energy: 81.7787 kcal/mole



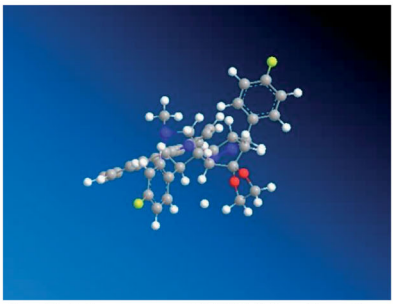
6b: Total energy: 64.0221 kcal/mole



6c: Total energy: 71.1936 kcal/mole



6d: Total energy: 64.2067 kcal/mol



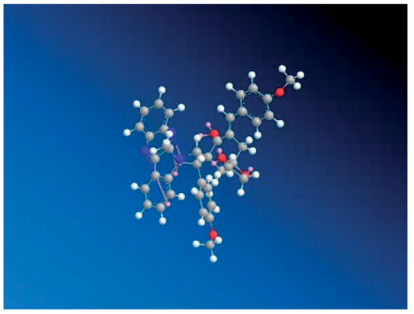
6e: Total energy: 63.0610 kcal/mole

Figure 2. Energy minimized structure of the product **6a–e**.

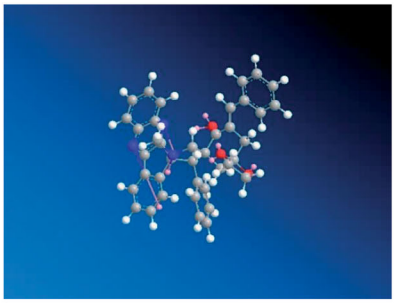
and the bis-cycloadduct **13a–e**, it is evident that the expected product **6a–e** formed has minimum energy when compared to the **12a–e** and **13a–e** favoring its formation as shown in Figs. 2–4, respectively.

Conclusion

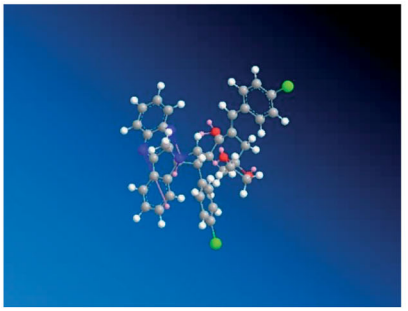
In conclusion, we have synthesized a series of novel pyrazolo-1,4-dioxa-spiro[4,5]decane grafted spiro-indenoquinoxaline pyrrolidines *via* a facile one-pot sequential five-component reaction involving [3 + 2]- cycloaddition reaction of azomethine ylides to various 7, 9-bis-



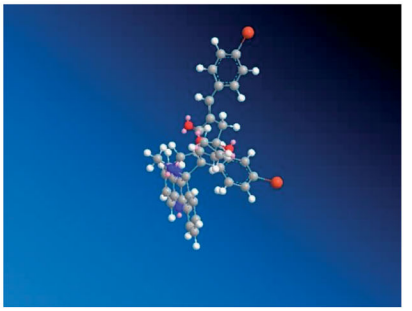
12a: 90.7077 kcal/mol



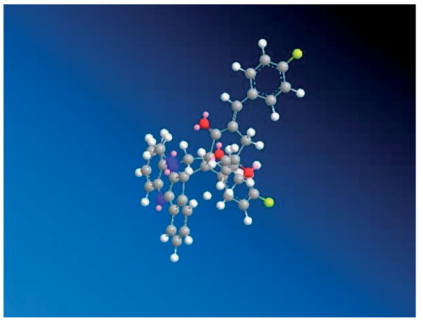
12b: 74.8893 kcal/mol



12c: 90.7279 kcal/mol



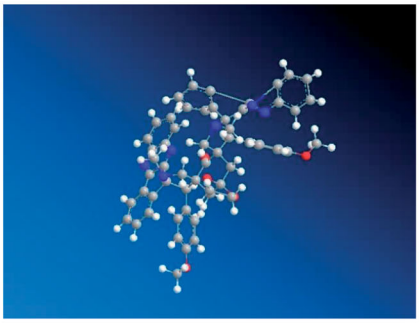
12d: 79.1417 kcal/mol



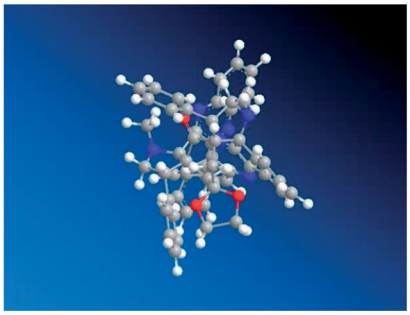
12e: 77.9248 kcal/mol

Figure 3. Energy minimized structure of **12a–e**.

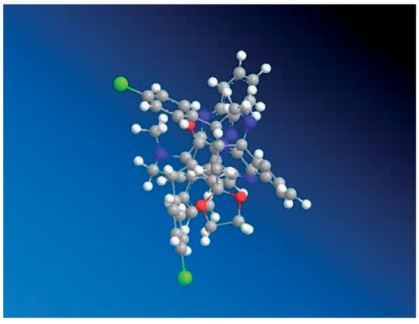
[(*E*)-arylmethylidene]-1.4-dioxa-spiro[4,5]-decan-8-one derivatives followed by ring annulation using hydrazine hydrate. The synthesized compounds carry diverse substitution pattern by choice. This method offers several advantages including its operational simplicity, selectivity with enhanced reaction rate in a one-pot five-component approach, mild reaction conditions, easy workup, affording the desired products from readily and cheaply available starting materials in a single step. A theoretical approach is provided for the formation of the product. The biological studies on these novel compounds are in progress and will be published elsewhere. We believe that this methodology will be useful for modern drug discovery program involving MCRs.



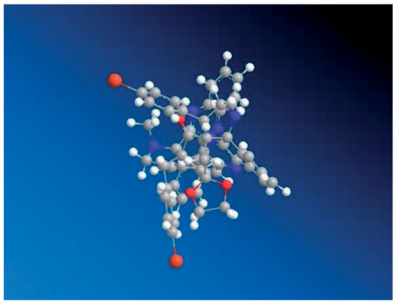
13a: 1107.0776 kcal/mol



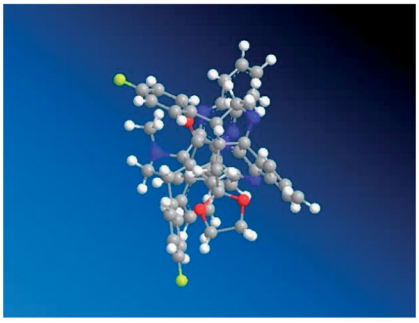
13b: 1104.2096 kcal/mol



13c:1010.6278 kcal/mol



13d: 1190.2017 kcal/mol



13e: 1090.7077 kcal/mol

Figure 4. Energy minimized structure of **13a–e**.

Experimental section

General considerations

All melting points are uncorrected. IR spectra were recorded on a SHIMADZU 8300 series FT-IR instrument. ^{1}H NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on a BRUKER 300 spectrometer at 300 MHz. ^{13}C NMR was recorded on a BRUKER 300 spectrometer at 75 MHz. High-resolution mass spectra were recorded on a JEOL-GC-MATE II mass spectrometer (70 Energy eV, Quadrapole double-focusing mass analyzer with photomultiplier tube detector). Column chromatography was performed on silica gel (ACME, 100–200 mesh). Solvents were reagent grade and were

purified according to standard procedures. The starting materials cyclohexanone monoacetal ketal, benzaldehyde, and its derivatives, 1,2-phenylenediamine, ninhydrin, sarcosine, hydrazine hydrate were purchased commercially and used as such. Cyclohexanone monoacetal ketal-based dipolarophiles were synthesized as per the literature procedures.[27]

Representative procedure for the synthesis of pyrazolo-1,4-dioxa-spiro[4,5]decane grafted trispiro-indenoquinoxaline pyrrolidine heterocycles 6a-e

A mixture of ninhydrin (1 mmol) and 1,2-phenylenediamine (1 mmol) was refluxed for 10 min in 10 ml of methanol followed by the addition of sarcosine (1 mmol). To this mixture, a solution of dipolarophile **1a** (1 mmol) in 10 ml of methanol was added. The mixture was refluxed until completion of the reaction as evidenced by TLC in petroleum ether-ethyl acetate mixture (3.5:1.5) and visualization was accomplished in an iodine chamber. Then to the reaction mixture, hydrazine hydrate (1 mmol) was added and refluxed for 1 h. After the completion of the reaction as evidenced by TLC, the solvent was removed under reduced pressure and the crude product **6a** was further purified by column chromatography using petroleum ether-ethyl acetate mixture (4:1) as eluent.

Spectral data of the representative product

1-N-Methyl-spiro-[2.11′]oxindole-spiro[3.7″][3″-(*p*-methoxyphenyl)]-1,4 -dioxospiro[4″,5″] decane-$\Delta^{1'',7''}$a-hexahydro-2H-indazole-4-(*p*-methoxyphenyl)-pyrrolidine 6a Color: green (amorphous solid); IR (KBr): (νC = N) 1605, (νNH) 3317 cm^{-1}, ^{1}H NMR ($CDCl_3$/300 MHz): ^{1}H NMR ($CDCl_3$/300 MHz): δ 1.01–1.19 (m, 2H), 1.38–1.46 (m, 1H), 1.77 (s, 3H, -NCH_3), 2.06–2.10 (m, 1H), 2.17–2.21 (m, 2H), 2.87 (q, *J*= 5.7 Hz, 1H), 3.00 (q, *J*= 5.7 Hz, 1H), 3.19 (q, *J*= 6.0 Hz, 1H), 3.55 (t, *J*= 8.2 Hz, 1H), 3.79 (s, 3H, -OMe), 3.84 (s, 3H, -OMe), 4.14 (t, *J*= 10.0 Hz, 1H), 4.28 (d, *J*= 13.2 Hz, 1H), 5.14 (dd, *J*= 7.6 Hz, 3.3 Hz, 1H), 6.02 (bs, 1H, -NH), 6.84 (d, *J*= 8.4 Hz, 2H), 6.95 (d, *J*= 8.4 Hz, 2H), 7.26 (t, *J*= 8.4 Hz, 2H), 7.49 (t, *J*= 7.3 Hz, 1H), 7.61–7.74 (m, 5H), 7.84 (d, *J*= 7.8 Hz, 1H), 8.09 (t, *J*= 4.9 Hz, 2H), 8.22–8.26 (m, 1H); ^{13}C NMR ($CDCl_3$/75 MHz): δ 30.92, 34.63, 39.04, 40.42, 49.85, 52.02, 55.31, 55.46, 59.45, 63.64, 64.45, 73.26, 78.18, 108.33, 121.03, 128.39, 128.79, 128.84, 129.02, 129.24, 129.68, 131.32, 131.57, 132.07, 132.30, 139.30, 140.24, 141.20, 147.55, 155.92, 157.99, 158.52, 159.22, 163.91 ppm; HRMS calculated for $C_{41}H_{39}N_5O_4$: 665.7738, Found: 665.7739 (M^+).

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