1,3-Dipolar cycloaddition approach to novel dispiro[pyrazolidine-4,3'-pyrrolizidine-2',3''-indoline]-2'',3,5-triones

Essam M. Hussein[a,b]*, Saleh A. Ahmed[a,b], Nizar El Guesmi[a,c] and Khalid S. Khairou[a]

[a]*Chemistry Department, Faculty of Applied Science, Umm Al-Qura University, 21955 Makkah, Saudi Arabia*
[b]*Chemistry Department, Faculty of Science, Assiut University, 71516 Assiut, Egypt*
[c]*Département de chimie, Faculté des Sciences de Monastir, Avenue de l'Environnement, 5019 Monastir, Tunisia*

A simple and convenient 1,3-dipolar cycloaddition of non-stabilised azomethine ylides derived from isatins and L-proline, in a variety of different solvents, to (*Z*)-4-arylidene-1-phenylpyrazolidine-3,5-diones as dipolarophiles afforded a series of novel dispiro[pyrazolidine-4,3'-pyrrolizidine-2',3''-indoline]-2'',3,5-triones regioselectively and in good yields.

Keywords: 1,3-dipolar cycloaddition, spiroheterocycles, 1-phenylpyrazolidine-3,5-dione, azomethine ylides, dipolarophile, regioselective synthesis

1,3-Dipolar cycloadditions are an important group of reactions in organic synthesis for building five- membered heterocycles especially substituted pyrrolidine, pyrrolizine, and pyrrolothiazole derivatives.[1–5] The cycloadditions of azomethine ylides which represent one of the most reactive and versatile classes of 1,3-dipoles are trapped readily by a range of dipolarophiles, either intra- or intermolecularly. The use of exocyclic olefins enables the construction of functionalised five-membered spiro heterocycles.[5–11] *N*-Arylpyrazoles are a very exciting class of heterocyclic compounds that have potent pharmacological activities in many medical fields such as hypoglycemic,[12] antibacterial, antifungal,[13] anti-tumor,[14] anti-thromboembolic disorders, antiangiogenic[15] and anti-inflammatory effects.[16,17] Pyrrolidine, pyrrolizine, and pyrrolothiazole derivatives are important bioactive heterocyclic compounds which have antimicrobial, antiviral, anti-inflammatory, antitubercular, anticancer, and antidiabetic activities.[18–21] In the present paper, we extend our previous studies on the synthesis of bioactive spiroheterocycles,[22–26] and now report a 1,3-dipolar cycloaddition reaction involving the exocyclic olefinic linkage derived from 1-phenylpyrazolidine-3,5-dione **2a–e**[5] to synthesise a series of novel dispiro[pyrazolidine-4,3'-pyrrolizine-2',3''-indoline]-2'',3,5-triones **5a–j** regioselectively in good to excellent yields through 1,3-dipolar cycloaddition reaction of azomethine ylides produced *in situ via* decarboxylative condensation of L-proline **3** and isatins **4a** and **4b** (Scheme 2)**.**

Results and discussion

1-Phenylpyrazolidine-3,5-dione **1** was prepared according to the cyclocondensation reaction of malonic acid and phenylhydrazine in the presence of phosphorus oxychloride; the different substituted (*Z*)-4-arylidene-1-phenylpyrazolidine-3,5-dione derivatives **2a–e**[27] were prepared in accordance with the previously reported procedure (Scheme 1).[5,28]

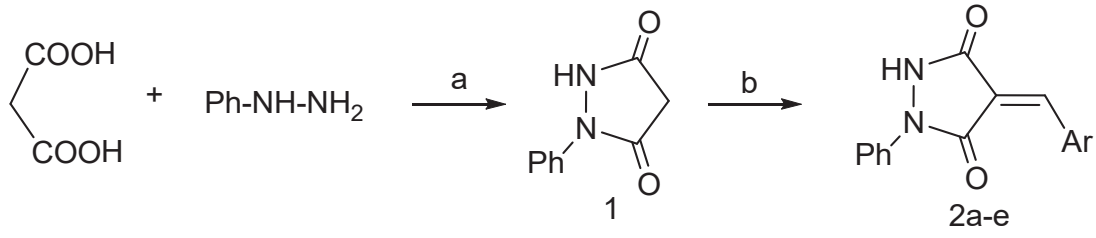
Effect of solvents

To study the effect of the solvent, the reaction of (*Z*)-4-(4-methoxybenzylidene)-1-phenylpyrazolidine-3,5-dione **2a**, L-proline **3** and isatin **4a** was designated as the model reaction. To promote the cycloaddition, various solvents such as, ethanol, methanol, 2-propanol, acetonitrile, 1,4-dioxane, and tetrahydrofuran were examined under reflux conditions and were shown to have a considerable impact on the yield of the reaction. The cycloaddition adduct was obtained in good yields, 76% and 83%, when the reaction was performed in ethanol and methanol, respectively (Table 1, entries 1 and 2). Moderate yields were obtained when 2-propanol (71%) and acetonitrile (69%) were used as solvent and the reaction time was extended (Table 1, entries 3 and 4). The yield decreased and a further increase in reaction time was required to drive the reaction

Table 1 Effect of the reaction medium on the synthesis of compound **5a**

Entry	Solvent	Time (h)	Yield (%)[a,b]
1	Ethanol	10	76
2	Methanol	10	83
3	2-propanol	15	71
4	Acetonitrile	15	69
5	Dioxane	20	52
6	Tetrahydrofuran	20	60

[a]Reaction conditions: 4-(*p*-methoxyphenyl)-1-phenylpyrazolidine-3,5-dione (**2a**) (1 mmol), L-proline (**3**) (1 mmol) and isatin (**4a**) (1 mmol); [b]Isolated yield.



2a; Ar = 4-$MeOC_6H_4$, 2b; Ar = 4-HOC_6H_4, 2c; Ar = 4-$(Me_2)NC_6H_4$
2d; Ar = 4-ClC_6H_4, 2e; Ar = 4-$O_2NC_6H_4$

Scheme 1 Synthesis of 1-phenylpyrazolidine-3,5-dione (**1**) and 4-arylidene-1-phenylpyrazolidine-3,5-dione derivatives **2a–e**: (a) $POCl_3$, $CHCl_3$, reflux, 2 h; (b) aromatic aldehydes, dioxane, reflux, 0.5 h.

* Correspondent. E-mail: essam.hussein78@yahoo.com

forward when 1,4-dioxane (52%) and tetrahydrofuran (60%) were used as solvents (Table 1, entries 5 snd 6). This effect is related to the increased stability of the polar transition states and/or intermediates involved in this reaction by increasing the polarity of the solvent (methanol > ethanol > 2-propanol > acetonitrile > tetrahydrofuran >1,4-dioxane).

Consequently, the best results with high yields of the product were obtained by refluxing the reaction mixture in methanol as solvent which provided the maximum yield within a reasonable time. The cycloaddition reaction of (*Z*)-4-(*p*-methoxyphenyl)-1-phenylpyrazolidine-3,5-dione **2a** as dipolarophile, L-proline **3**, and isatin **4a** was carried out to afford the spirocycle **5a** as a single regioisomer, as indicated by TLC, in a highly regioselective manner. To assess the feasibility of the reaction, the azomethine ylides generated by decarboxylative condensation of L-proline **3** and isatins **4a** and **4b** were treated with various dipolarophiles (*Z*)-4-arylidene-1-phenylpyrazolidine-3,5-dione derivatives **2a–e** (Scheme 2).

Under optimised conditions, the reaction proceeded easily to afford a series of novel 4'-(aryl)-dispiro[pyrazolidine-4,3'-pyrrolizine-2',3''-indoline]-2'',3,5-triones **5a–j** in good to excellent yields (70–93%). The results are given in Table 2.

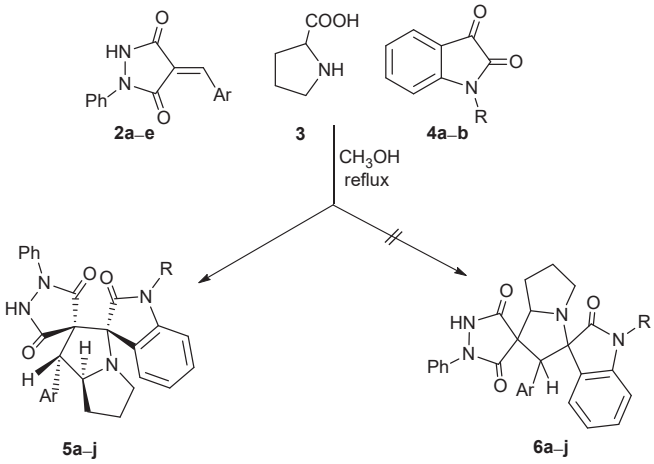
As shown in Scheme 3, the reaction proceeds through the generation of an azomethine ylide *via* the decarboxylative condensation of isatins **4a–b** with L-proline **3**. This cycloaddition is regioselective with the electron-rich carbon of the dipole adding to the β-carbon of the α,β-unsaturated moiety of **2a–e**. The regioselectivity in the product formation can be explained by considering secondary interactions of the orbitals of the C_5-carbonyl group of (*Z*)-4-arylidene-1-phenylpyrazolidine-3,5-diones **2a–e** with those of the azomethine ylide as shown in Scheme 4. Accordingly, the observed regioisomer **5a–j** through path A is more favourable than **6a–j** due to the secondary orbital interaction (SOI)[29] which is not possible in path B. Hence, only one regioisomer **5a–j** was formed as established by NMR analysis.

The structures of the isolated products were confirmed to be dispiro[pyrazolidine-4,3'-pyrrolizidine-2',3''-indoline]-2'',3,5-triones **5a–j** rather than the other regioisomer dispiro[pyrazolidine-4,4'-pyrrolizidine-2',3''-indoline]-2'',3,5-triones **6a–j** based on spectroscopic (^{1}H, ^{13}C NMR) data.

The ^{1}H NMR spectrum of **5a**, as a representative example, revealed the presence of three multiplet signals in the regions 1.80–1.95, 2.00–2.18, and 2.58–2.65 ppm for 6'-CH_2, 5'-CH_2, and 7'-CH_2 protons respectively. A singlet at 3.68 ppm, corresponds to the methoxy group protons. The 4'a-CH proton exhibited a multiplet in the region 4.53–4.63 ppm. The methine proton (4'-CH) exhibited a doublet signal at 3.88 ppm (J = 15 Hz) on the basis of its multiplicity, excluding the formation of the other regioisomeric form **6a–j**.

If the other isomers **6a–j** were formed, one would expect a singlet rather than a doublet for the pyrrolizidinyl methine proton.

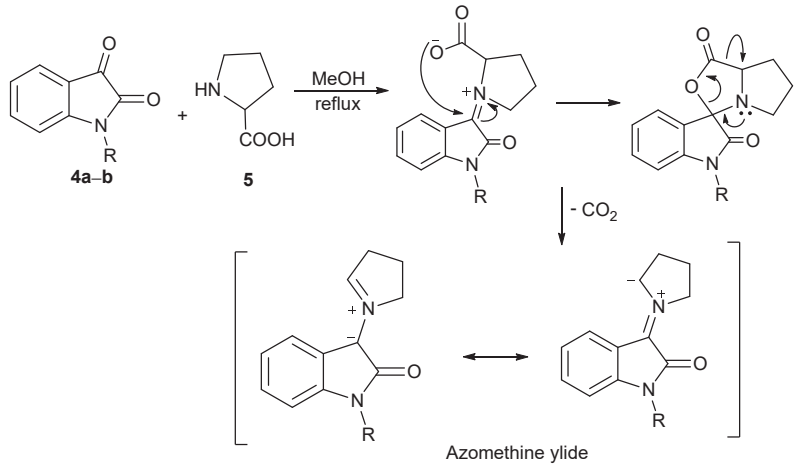
The ^{13}C NMR spectrum added conclusive support to proposed structure of the spirocycloadduct **5a**. The two spiro



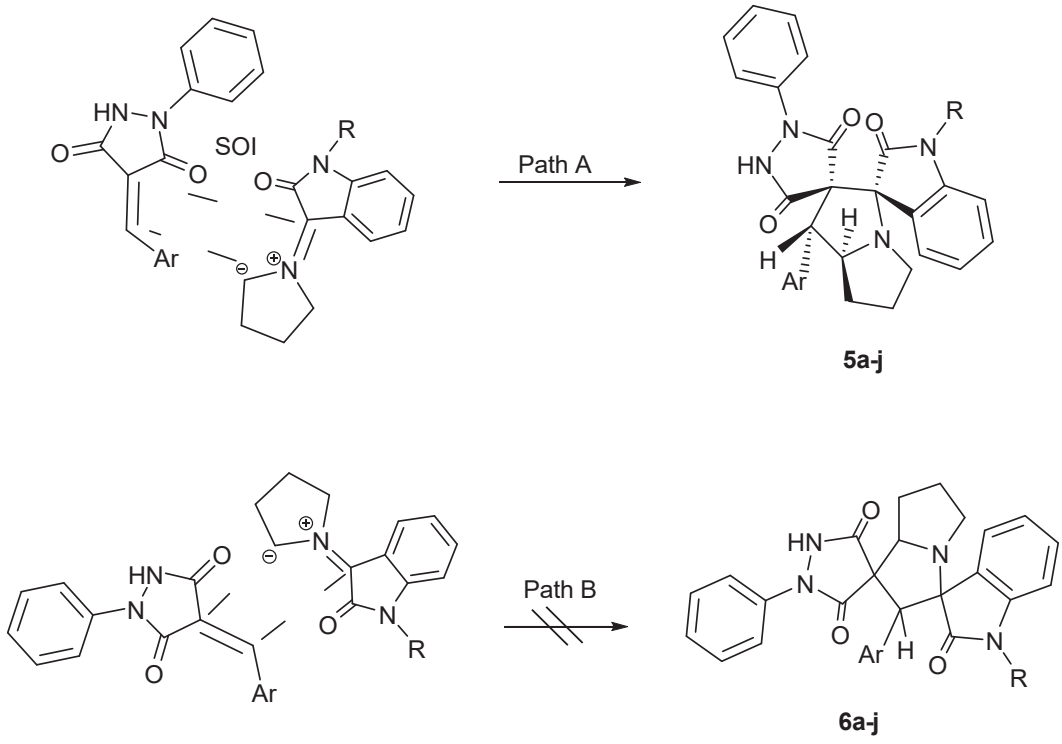
Scheme 2 Synthesis of dispiro[pyrazolidine-4,3'-pyrrolizine-2',3''-indoline]-2'',3,5-triones **5a–j**.

Table 2 Synthesis of dispiro[pyrazolidine-4,3'-pyrrolizidine-2',3''-indoline]-2'',3,5-triones (**5a–j**)

Entry	Product	R	Ar	Time (h)	Yield (%)
1	**5a**	H	4-$MeOC_6H_4$	10	83
2	**5b**	H	4-HOC_6H_4	12	81
3	**5c**	H	4-$(CH_3)_2NC_6H_4$	13	71
4	**5d**	H	4-ClC_6H_4	9	86
5	**5e**	H	4-$O_2NC_6H_4$	7	93
6	**5f**	CH_3	4-$MeOC_6H_4$	12	80
7	**5g**	CH_3	4-HOC_6H_4	12	79
8	**5h**	CH_3	4-$(CH_3)_2NC_6H_4$	14	70
9	**5i**	CH_3	4-ClC_6H_4	10	84
10	**5j**	CH_3	4-$O_2NC_6H_4$	9	91



Scheme 3 Mechanistic representation for formation of azomethine ylide.



Scheme 4 Mode of approach of azomethine ylide.

carbons resonated at 67.87 and 75.72 ppm. The carbonyl carbon resonated at 176.32 ppm, respectively. The signals at 30.49, 31.30, 47.02, 51.08, 55.43, and 56.24 ppm are assigned to 6'-CH_2, 5'-CH_2, 7'-CH_2, 4'-CH, CH_3, and 4'a-CH carbons, respectively.

Theoretical studies based on DFT reactivity indices

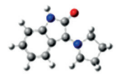
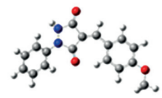
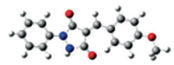
Recent studies have shown that, different chemical reactivity descriptors have been developed to understand and predict chemical reactivity. Some reactivity indexes can be defined within the DFT theory which are very useful for predicting the feasibility of 1,3-dipolar cycloaddition and Diels–Alder reactions.[30–36] These include the global electrophilicity index, ω, introduced by Parr and defined by Eqn (1)[37–39] In this equation, the electronic chemical potential μ and the chemical hardness η of a substrate are two parameters which were evaluated in terms of the one-electron energies of the frontier molecular orbitals (FMOs) *i.e.* the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) at the ground state of the molecules: $\mu = ½(\varepsilon_H + \varepsilon_L)$; $\eta = (\varepsilon_L - \varepsilon_H)$.[36–38] Another informative index used by Domingo *et al.* is called ΔN_{max} parameter, defined by Eqn (2), which is a measure of the maximum amount of electronic charge that the electrophilic partner can accept.[37] Calculated values ω, μ, η, and ΔN_{max} of relevance for the study are collected in Table 3.

$$\omega = \mu^2/2\eta \quad (1)$$

$$\Delta N_{max} = -\mu/\eta \quad (2)$$

From the values of electrophilicity indices (ω) respresented in Table 1, the (Z)-dipolarophile, in comparison with azomethine ylide and (E)-dipolarophile, acts as an electrophile due to the larger value of its ω. On the other hand, 1,3-dipolar cycloadditions are HOMO–LUMO controlled reactions where the reactivity depends on the nature of the dipole and dipolarophile and the energy gap between the HOMO and LUMO orbitals. 1,3-Dipolar cycloaddition reactions for azomethine ylide substrates are typical of 1,3-dipolar

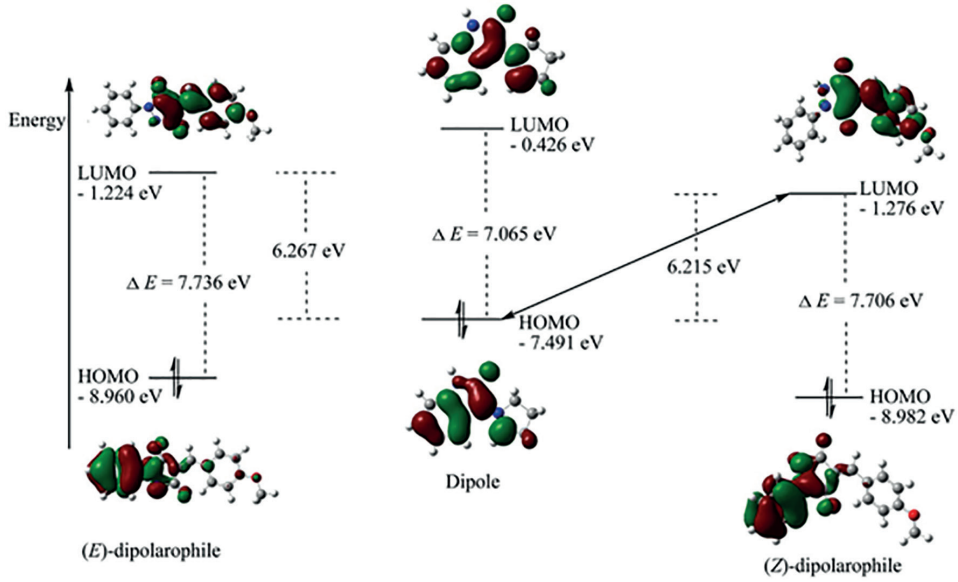
Table 3 Frontier molecular orbitals energy ε_H and ε_L, electronic chemical potential μ, chemical hardness η, global electrophilicity ω, and ΔN_{max} parameter for dipoles and dipolarophiles (compound **2a** is given as an example)[a]

		e_H[b]	e_L[b]	μ	η	ω	ΔN_{max}
Dipole		−0.2753	−0.0156	−0.1455	0.2596	1.109	0.56
Dipolarophile	 (*Z*) form	−0.3301	−0.0469	−0.1885	0.2832	1.707	0.67
	 (*E*) form	−0.3293	−0.0450	−0.1871	0.2842	1.675	0.65

[a]Frontier molecular orbitals energy ε_H and ε_L, electronic chemical potential μ and chemical hardness η in atomic units; global electrophilicities ω in eV as defined by Eqn 1; ΔN_{max} in electron units; [b]All computations were carried out with the Gaussian 03 suite of programs.[46] Calculations based on the method of DFT were performed using the B3LYP exchange correlation functional, together with the standard 6-31G basis set.

cycloadditions of type I.[40–44] In type I, 1,3-dipolar cycloaddition reactions the predominant frontier molecular orbital (FMO) interaction is that of $HOMO_{dipole}$ with the $LUMO_{dipolarophile}$.[45] As shown in scheme 5, the (*Z*)-dipolarophile has a lower energy gap ($\Delta E = E_{LUMO} - E_{HOMO} = 7.706$ eV) than the energy gap of the corresponding (*E*)-form ($\Delta E = 7.736$ eV), thus, $HOMO_{dipole}$–$LUMO_{(Z)\text{-dipolarophile}}$ interaction is favourable based on the lowest energy gap ($\Delta E = E_{LUMO\text{-}(Z)\text{-}dipolarophile} - E_{HOMO\text{-}dipole} = 6.215$ eV).

Recent investigations have used the ω values to classify dipole and dipolarophiles on a unique scale.[30–39] According to this model, the polar character of a dipole-dipolarophile interaction can be assessed from the difference, Δω, in the global electrophilicities of the two reagents as well as the ΔN_{max} values for the system at hand. Thus, it can be safely anticipated



Scheme 5 Typical 1,3-dipolar cycloaddition reactions on the basis of the FMOs: $HOMO_{dipole}$-$LUMO_{dipolarophile}$ interaction.

that reactions involving a dipole and a dipolarophile located at the ends of the ω scale will proceed with an especially strong polar character. [30–39] In turn, reactions associated with small Δω values should be prototypes of non-polar processes. It is clear that, the 1,3-dipolar cycloaddition of azomethine ylide with (*Z*)-4-arylidene-1-phenylpyrazolidine-3,5-diones as dipolarophiles (Δω = 0.6 << 4.5 eV) is a reaction governed by a concerted mechanism. Also, the stereo-configuration of the cycloadduct is confirmed by some theoretical studies on all 16 possible stereoisomers (see the supplementary infomation) of the selected compound **5a**. The calculated heat of formation (Δ*H*) and total energy of **5a** showed that the most stable form (the lowest heat of formation with lowest total energy) is 2'*R*,3'*R*,4'*R*,4'a*S* (Δ*H* = 42.392 kcal mol^{-1} with total energy = 33.686 kcal mol^{-1}).

Conclusions

In conclusion, we have synthesised a series of novel dispiro[pyrazolidine-4,3'-pyrrolizidine-2',3''-indoline]-2'',3,5-triones through 1,3-dipolar cycloaddition of azomethine ylides generated *in situ via* decarboxylative condensation of isatin derivatives and L-proline with various (*Z*)-4-arylidene-1-phenylpyrazolidine-3,5-dione derivatives dipolarophiles in methanol as suitable reaction medium. This method has the advantages of operational simplicity, easy workup, mild reaction conditions, high atom economy, and good to excellent yields. The reactions proceed in a regio- and stereoselective manner.

Experimental

All melting points were uncorrected and measured on Stuart (SMP3) melting point apparatus. FTIR spectra were recorded on Shimadzu IR-3600 spectrometer. Elemental analyses (C, H, N, and Cl) were performed on an Elementar GmbH VarioEL V2:3 instrument; the results were found to be in good agreement with the calculated values. NMR was recorded on a Bruker Avance 500 MHz with DMSO–d_6 as solvent. All the reagents and solvents used were of high grade and purchased from Sigma-Aldrich.

*Synthesis of dispiro[pyrazolidine-4,3'-pyrrolizidine-2',3''-indoline]-2'',3,5-triones (***5a–j***); general procedure*

A mixture of the appropriate dipolarophile **2** (0.294 g, 1 mmol), isatin **4a** (0.147 g, 1 mmol) and L-proline (0.115 g, 1 mmol) was refluxed in methanol (15 mL) for 10 h, (Table 2). Upon completion (monitored by TLC), the reaction mixture was allowed to cool to room temperature. The solvent was concentrated under reduced pressure and the solid product was filtered off and crystallised from methanol to afford the pure compound **5**.

(2'R*,3'R*,4'R*,4'aS*)-*4'-(*p-*Methoxyphenyl)-1-phenyldispiro[pyrazolidine-4,3'-pyrrolizidine-2',3''-indoline]-2'',3,5-trione* (**5a**): Orange crystals; m.p. 160-161 °C (MeOH); FTIR (ν_{max}/cm^{-1}) KBr: 3210 (NH), 3067 (C–H_{arom}), 2958 (C–H_{aliph}), 1701 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.80–1.95 (2H, m, 6'-CH_2), 2.00–2.18 (2H, m, 5'-CH_2), 2.58–2.65 (2H, m, 7'-CH_2), 3.68 (3H, s, CH_3), 3.88 (1H, d, 4'-CH, *J* = 15.0 Hz), 4.53–4.63 (1H, m, 4'a-CH), 6.60–7.85 (13H, m, ArH), 10.47 (1H, s, NH), 10.53 (1H, s, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 30.49 (CH_2), 31.30 (CH_2), 47.02 (CH_2), 51.08 (CH), 55.43 (CH_3), 56.24 (CH), 67.87 (spiro-C), 75.72 (spiro-C), 109.90, 114.34, 114.95, 118.77, 121.88, 126.06, 127.77, 129.23, 129.43, 129.78, 130.13, 137.71, 142.54, 142.73, 159.04, 176.32 (C=O), 191.31 (C=O); Anal. calcd for $C_{29}H_{26}N_4O_4$: C, 70.43; H, 5.30; N, 11.33; found: C, 70.53; H, 5.09; N, 11.20%.

(2'R*,3'R*,4'R*,4'aS*)-*4'-(*p-*Hydroxyphenyl)-1-phenyldispiro[pyrazolidine-4,3'-pyrrolizidine-2',3''-indoline]-2'',3,5-trione* (**5b**): Pale red crystals; m.p. 174–175 °C (MeOH); FTIR (ν_{max}/cm^{-1}) KBr: 3350–2810 (br, NH, OH), 1700 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.35–1.70 (2H, m, 6'-CH_2), 1.75–2.00 (2H, m, 5'-CH_2), 2.15–2.45 (2H, m, 7'-CH_2), 3.85–4.60 (2H, m, 4'-CH, 4'a-CH), 6.50–7.30 (4H, m, ArH), 7.50–8.70 (9H, m, ArH), 9.58 (1H, s, OH), 10.25–10.26 (2H, m, 2 × NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 27.71 (CH_2), 30.43 (CH_2), 47.45(CH_2), 52.06 (CH), 65.65 (CH), 72.46 (spiro-C), 73.11 (spiro-C), 110.36, 123.59, 123.95, 124.19, 126.67, 127.67, 129.79, 130.10, 130.24, 130.31, 142.41, 146.94, 148.95, 178.97 (C=O), 199.82 (C=O); Anal. calcd for $C_{28}H_{24}N_4O_4$: C, 69.99; H, 5.03; N, 11.66; found: C, 69.70; H, 4.90; N, 11.45%.

(2'R*,3'R*,4'R*,4'aS*)-*4'-(*p-*Dimethylaminophenyl)-1-phenyldispiro[pyrazolidine-4,3'-pyrrolizidine-2',3''-indoline]-2'',3,5-trione* (**5c**): Pale red crystals; m.p. 181–182 °C (MeOH/n-hexane, 5:1); FTIR (ν_{max}/cm^{-1}) KBr: 3189 (NH), 3030 (C–H_{arom}), 2960 (C–H_{aliph}), 1698 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.43–1.66 (2H, m, 6'-CH_2), 1.74–1.92 (2H, m, 5'-CH_2), 2.83–3.01 (2H, m, 7'-CH_2), 3.10–3.19 (2H, m, 4'a-CH), 3.36 (6H, s, 2 × CH_3), 3.75 (1H, d, 4'-CH, *J* = 10.0 Hz), 6.58–7.83 (8H, m, ArH), 8.09–8.60 (7H, m, ArH, 2 × NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 25.23 (CH_2), 27.35 (CH_2), 30.68 (CH_2), 51.34 (CH_3), 55.48 (CH), 58.94 (CH), 68.46 (spiro-C), 72.94 (spiro-C), 108.15, 109.05, 113.84, 114.50, 121.80, 129.28, 129.94, 132.53, 134.06, 143.41, 143.88, 158.56, 173.93, 177.31 (C=O), 199.65 (C=O), 202.98 (C=O); Anal. calcd for $C_{30}H_{29}N_5O_3$: C, 70.99; H, 5.76; N, 13.80; found: C, 70.70; H, 5.60; N, 13.52%.

(2'R*,3'R*,4'R*,4'aS*)-*4'-(*p-*Chlorophenyl)-1-phenyl-dispiro[pyrazolidine-4,3'-pyrrolizidine-2',3''-indoline]-2'',3,5-trione* (**5d**): Pale brown crystals; m.p. 170–171 °C (MeOH); FTIR (ν_{max}/cm^{-1}): 3161 (NH), 3025 (C–H$_{arom}$), 2980 (C–H$_{aliph}$), 1690 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.82–2.19 (4H, m, 5'-CH$_2$, 6'-CH$_2$), 2.53–2.58 (2H, m, 7'-CH$_2$), 3.05–3.18 (1H, m, 4'a-CH), 3.64 (1H, d, 4'-CH, *J* = 10.0 Hz), 6.83–7.53 (13H, m, ArH), 7.87 (1H, s, NH), 7.89 (1H, s, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 26.43 (CH$_2$), 30.51 (CH$_2$), 31.29 (CH$_2$), 51.27 (CH), 55.43 (CH), 70.84 (spiro-C), 75.23 (spiro-C), 108.67, 114.37, 114.99, 122.58, 122.69, 125.72, 129.75, 130.35, 132.31, 144.06, 159.04, 174.85 (C=O), 191.83 (C=O); Anal. calcd for $C_{28}H_{23}ClN_4O_3$: C, 67.40; H, 4.65; Cl, 7.11; N, 11.23; found: C, 67.16; H, 4.40; Cl, 7.00; N, 11.00%.

(2'R*,3'R*,4'R*,4'aS*)-*4'-(*p-*Nitrophenyl)-1-phenyl-dispiro[pyrazolidine-4,3'-pyrrolizidine-2',3''-indoline]-2'',3,5-trione* (**5e**): Pale brown crystals; m.p. 190–191 °C (MeOH); FTIR (ν_{max}/cm^{-1}): 3200 (NH), 3041 (C–H$_{arom}$), 2990 (C–H$_{aliph}$), 1700 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.86–2.02 (4H, m, 2 × CH$_2$), 2.20–2.60 (2H, m, 7'-CH$_2$), 4.69–4.74 (1H, m, 4'a-CH), 4.79 (1H, d, 4'-CH, *J* = 10.0 Hz), 6.69–7.47 (9H, m, ArH), 7.58 (2H, d, ArH, *J* = 10.0 Hz), 8.17 (2H, d, ArH, *J* = 10.0 Hz), 10.58 (1H, s, NH), 10.65 (1H, s, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 30.56 (CH$_2$), 31.31 (CH$_2$), 47.01 (CH$_2$), 50.92 (CH), 67.54 (CH), 70.29 (spiro-C), 75.85 (spiro-C), 109.93, 120.00, 124.16, 126.01, 129.33, 130.02, 130.39, 141.14, 142.79, 147.37, 176.13, 176.29 (C=O), 191.62 (C=O); Anal. calcd for $C_{28}H_{23}N_5O_5$: C, 66.00; H, 4.55; N, 13.75; found: C, 65.73; H, 4.31; N, 13.54%.

(2'R*,3'R*,4'R*,4'aS*)-*4'-(*p-*Methoxyphenyl)-1''-methyl-1-phenyl-dispiro[pyrazolidine-4,3'-pyrrolizidine-2',3''-indoline]-2'',3,5-trione* (**5f**): Orange crystals; m.p. 151–152 °C (MeOH); FTIR (ν_{max}/cm^{-1}): 3100 (NH), 3050 (C–H$_{arom}$), 2941 (C–H$_{aliph}$), 1696 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.70–1.85 (2H, m, 6'-CH$_2$), 1.95–2.20 (2H, m, 5'-CH$_2$), 2.56–2.68 (2H, m, 7'-CH$_2$), 3.61 (3H, s, CH$_3$), 3.75–3.89 (4H, m, CH$_3$, 4'-CH), 4.14–4.28 (1H, m, 4'a-CH), 6.67–7.89 (13H, m, ArH), 9.87 (1H, s, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 27.63 (CH$_2$), 31.32 (CH$_2$), 47.02 (CH$_2$), 51.08 (CH), 55.41 (CH$_3$), 56.31 (CH), 67.89 (spiro-C), 75.72 (spiro-C), 109.90, 114.35, 114.95, 118.70, 122.50, 127.03, 127.97, 129.23, 129.43, 129.78, 130.13, 137.71, 142.54, 143.70, 159.04, 176.32 (C=O), 195.63 (C=O); Anal. calcd for $C_{30}H_{28}N_4O_4$: C, 70.85; H, 5.55; N, 11.02; found: C, 70.58; H, 5.32; N, 10.80%.

(2'R*,3'R*,4'R*,4'aS*)-*4'-(*p-*Hydroxyphenyl)-1''-methyl-1-phenyl-dispiro[pyrazolidine-4,3'-pyrrolizidine-2',3''-indoline]-2'',3,5-trione* (**5g**): Orange crystals; m.p. 166–167 °C (MeOH); FTIR (ν_{max}/cm^{-1}): 3250–3105 (br, NH, OH), 3035 (C–H$_{arom}$), 2940 (C-H$_{aliph}$), 1700 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.82–1.90 (2H, m, 6'-CH$_2$), 2.15–2.45 (4H, m, 5'-CH$_2$, 7'-CH$_2$), 3.45 (3H, s, CH$_3$), 3.86–4.61 (2H, m, 4'-CH, 4'a-CH), 6.63–7.82 (13H, m, ArH), 9.68 (1H, s, OH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 26.45 (CH$_2$), 30.51 (CH$_2$), 31.29 (CH$_2$), 47.02 (CH), 51.47 (CH$_3$), 67.93 (CH), 70.87 (spiro-C), 75.15 (spiro-C), 108.76, 115.70, 116.51, 119.65, 122.58, 125.70, 129.29, 129.66, 130.33, 132.62, 138.29, 144.03, 157.14, 174.89 (C=O), 191.56 (C=O); Anal. calcd for $C_{29}H_{26}N_4O_4$: C, 70.43; H, 5.30; N, 11.33; found: C, 70.28; H, 5.11; N, 11.05%.

(2'R*,3'R*,4'R*,4'aS*)-*4'-(*p-*Dimethylaminophenyl)-1''-methyl-1-phenyl-dispiro[pyrazolidine-4,3'-pyrrolizidine-2',3''-indoline]-2'',3,5-trione* (**5h**): Pale brown crystals; m.p. 173–174 °C (MeOH/n-hexane, 3:1); FTIR (ν_{max}/cm^{-1}): 3170 (NH), 3073 (C–H$_{arom}$), 2911 (C–H$_{aliph}$), 1700 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.80–2.51 (6H, m, 3 × CH$_2$), 3.03 (1H, d, 4'-CH, *J* = 10.0 Hz), 3.14 (3H, s, CH$_3$), 3.57 (6H, s, 2 × CH$_3$), 4.00–4.05 (1H, m, 4'a-CH), 6.80 (2H, d, ArH, *J* = 10.0 Hz), 7.15–7.18 (2H, m, ArH), 7.37–7.44 (3H, m, ArH), 7.68–7.71 (4H, m, ArH), 7.74 (2H, d, ArH, *J* = 10.0 Hz), 8.58 (1H, s, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 27.16 (CH$_2$), 30.49 (CH$_2$), 35.82 (CH$_2$), 41.33 (CH$_3$), 51.08 (CH), 55.43 (CH$_3$), 56.04 (CH), 67.87 (spiro-C), 75.80 (spiro-C), 110.17, 111.30, 112.80, 118.77, 121.88, 126.06, 128.23, 129.23, 129.43, 129.78, 129.97, 138.73, 142.54, 142.73, 170.95, 176.32 (C=O), 191.63 (C=O); Anal. calcd for $C_{31}H_{31}N_5O_3$: C, 71.38; H, 5.99; N, 13.43; found: C, 71.19; H, 5.67; N, 13.10%.

(2'R*,3'R*,4'R*,4'aS*)-*4'-*(p-*Chlorophenyl)-1''-methyl-1-phenyl-dispiro[pyrazolidine-4,3'-pyrrolizidine-2',3''-indoline]-2'',3,5-trione* (**5i**): Grey crystals; m.p. 159–160 °C (MeOH); FTIR (ν_{max}/cm^{-1}): 3100 (NH), 3070 (C–H$_{arom}$), 2939 (C–H$_{aliph}$), 1690 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.71–1.88 (4H, m, 5'-CH$_2$, 6'-CH$_2$), 2.42–2.50 (2H, m, 7'-CH$_2$), 3.05–3.20 (1H, m, 4'a-CH), 3.41 (3H, s, CH$_3$), 3.60 (1H, d, 4'-CH, *J* = 10.0 Hz), 6.80–7.55 (13H, m, ArH), 9.09 (1H, s, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 27.34 (CH$_2$), 30.52 (CH$_2$), 47.04 (CH$_2$), 51.27 (CH), 54.41 (CH$_3$), 67.92 (CH), 70.88 (spiro-C), 75.23 (spiro-C), 108.67, 113.52, 114.99, 122.58, 122.69, 125.72, 129.75, 130.35, 133.31, 144.06, 159.04, 174.85 (C=O), 191.96 (C=O); Anal. calcd for $C_{29}H_{25}ClN_4O_3$: C, 67.90; H, 4.91; Cl, 6.91; N, 10.92; found: C, 67.59; H, 4.70; Cl, 6.60; N, 10.68%.

(2'R,3'R,4'R,4'aS)-*1''-Methyl-4'-(*p-*nitrophenyl)-1-phenyl-dispiro[pyrazolidine-4,3'-pyrrolizidine-2',3''-indoline]-2'',3,5-trione* (**5j**): Pale brown crystals; m.p. 178–179 °C (MeOH); FTIR (ν_{max}/cm^{-1}): 3202 (NH), 3053 (C–H$_{arom}$), 2932 (C–H$_{aliph}$), 1700 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.85–2.00 (4H, m, 2CH$_2$), 2.20–2.55 (2H, m, 7'-CH$_2$), 4.40–4.63 (4H, m, CH$_3$, 4'a-CH), 4.71 (1H, d, 4'-CH, *J* = 10.0 Hz), 6.67-7.46 (9H, m, ArH), 7.55 (2H, d, ArH, *J* = 10.0 Hz), 8.17 (2H, d, ArH, *J* = 10.0 Hz), 10.02 (1H, s, NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 27.51 (CH$_2$), 33.05 (CH$_2$), 47.02 (CH$_2$), 51.63 (CH), 52.91 (CH$_3$), 67.54 (CH), 71.25 (spiro-C), 75.89 (spiro-C), 108.90, 120.53, 125.05, 126.73, 129.45, 130.02, 131.35, 141.14, 142.88, 147.37, 176.32, 176.29 (C=O), 191.92 (C=O); Anal. calcd for $C_{29}H_{25}N_5O_5$: C, 66.53; H, 4.81; N, 13.38; found: C, 66.44; H, 4.52; N, 13.08%.

Electronic Supplementary Information

The ESI {Carteasan coordinates of optimised structures of dipole, dipolarophile and cycloadducts (both *R,R,R,S* and *S,S,S,R*) calculated by DFT} is available through stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data

Received 7 December 2016; accepted 9 May 2017
Paper 1604472
https://doi.org/10.3184/174751917X14951017434315
Published online: 22 May 2017

References

1 V. Nair and T.D. Suja, *Tetrahedron*, 2007, **63**, 12247.
2 M. Ghandi, A. Yari, S.J.T. Rezaei and A. Taheri, *Tetrahedron Lett*., 2009, **50**, 4724.
3 K.A. Ahrendt and R.M. Williams, *Org. Lett*., 2004, **6**, 4539.
4 S.V. Karthikeyan, B.D. Bala, V.P.A. Raja, S. Perumal, P. Yogeeswari and D. Sriram, *Bioorg. Med. Chem. Lett*., 2010, **20**, 350.
5 E.M. Hussein and M.I. Abdel-Monem, *Arkivoc*, 2011, **10**, 85.
6 I. Coldham and R. Hufton, *Chem. Rev*., 2005, **105**, 2765.
7 N.V. Lakshmi, P. Thirumurugan and P.T. Perumal, *Tetrahedron Lett*., 2010, **51**, 1064.
8 G.S. Singh and Z.Y. Desta, *Chem. Rev*., 2012, **112**, 6104.
9 F.Z. Macaev, N.S. Sucman and V.V. Boldescu, *Russ. Chem. Bull., Int. Ed*., 2014, **63**, 15.
10 M.M.M. Santos, *Tetrahedron*, 2014, **70**, 9735.
11 T.L. Pavlovska, R.G. Redkin, V.V. Lipson and D.V. Atamanuk, *Mol. Divers*., 2016, **20**, 299.
12 T. Maekawa, R. Hara, H. Odaka, H. Kimura, H. Mizufune and K. Fukatsu, PCT Int. Appl.WO 03 99,793, *Chem. Abstr*., 2004, **140**, 16723h.
13 S.M. Abdel-Gawad, A. Abdel-Aziem and M.M. Ghorab, *Phos. Sulf*., 2003, **178**, 1795.
14 M. Mercep, M. Mesic and D. Pesic, PCT Int. Appl. WO 03 99,822, *Chem. Abstr*., 2004, **140**, 16724j.
15 J.X. Qiao, D.J. Pinto, M.J. Orwat, W. Han and S.R. Friedrich, PCT Int. Appl. WO 03 99,276, *Chem. Abstr*., 2004, **140**, 16722g.
16 M.C. Cardia, L. Corda, A.M. Fadda, A.M. Maccioni, E. Maccioni and A. Plumitallo, *Farmaco*, 1998, **53**, 698.
17 M.D. Mullican, M.W. Wilson, D.T. Cannor, C.R. Kostlan and R.D. Dyer, *J. Med. Chem*., 1993, **36**, 1090.
18 R. Murugan, S. Anbazhagan and S.S. Narayanan, *Eur. J. Med. Chem*., 2009, **44**, 3272.
19 K. Karthikeyan, R.S. Kumar, D. Muralidharan and P.T. Perumal, *Tetrahedron Lett*., 2009, **50**, 7175.
20 A.S. Girgis, *Eur. J. Med. Chem*., 2009, **44**, 91.
21 R.R. Kumar, S. Perumal, S.C. Manju, P. Bhatt, P. Yogeeswari and D. Sriram, *Bioorg. Med. Chem. Lett*., 2009, **19**, 3461.
22 S.A. Abdel-Mohsen and E.M. Hussein, *Russ. J. Bioorg. Chem*., 2014, **40**, 343.

23 E.M. Hussein, G.S. Masaret and K.S. Khairou, *Chem. Cent. J.*, 2015, **9**:25, https://doi.org/10.1186/s13065-015-0101-8.
24 E.M. Hussein, H.F. Al-Shareef, A.H. Aboellil and H.A. Elhady, *Z. Naturforsch.*, 2015, **70**(b), 783.
25 H.F. Al-Shareef, A.H. Aboellil, H.A. Elhady and E.M. Hussein, *SpringerPlus*, 2016, **5**, 887.
26 M.A. Abdel-Rahman, E.M. Hussein and M.A. Hussein, *Des. Monomers Polym.*, 2016, **19**, 650.
27 G. Samala, S.S. Kakan, R. Nallangi, P.B. Devi, J.P. Sridevi, S. Saxena, P. Yogeeswari and D. Sriram, *Int. J. Mycobacteriol.*, 2014, **3**, 117.
28 D. Prelicz and B. Arct, *Acta Pol. Pharm.*, 1968, **25**, 207.
29 R.T. Pardasani, P. Pardasani, V. Chaturvedi, S.K. Yadav, A. Saxena and I. Sharma, *Heteroat. Chem.*, 2003, **14**, 36.
30 S. Lakhdar, F. Terrier, D. Vichard, G. Berionni, N. El Guesmi, R. Goumont and T. Boubaker, *Chem. Eur. J.*, 2010, **16**, 5681.
31 D.V. Steglenko, M.E. Kletsky, S.V. Kurbatov, A.V. Tatarov, V.I. Minkin, R.Goumont and F. Terrie, *J. Phys. Org. Chem.*, 2008, **22**, 298.
32 P. Arroyo, M.T. Picher and L.R. Domingo, *J. Mol. Struct.*, 2004, **709**, 45.
33 P. Arroyo, M.T. Picher, L.R. Domingo and F. Terrier, *Tetrahedron*, 2005, **61**, 7359.
34 L.R. Domingo, M.J. Aurell, P. Perez and R. Contreras, *Tetrahedron*, 2002, **58**, 4417.
35 L.R. Domingo, M.J. Aurell, P. Perez and R. Contreras, *Tetrahedron*, 2003, **59**, 3117.
36 L.R. Domingo, M.J. Aurell, P. Perez and R. Contreras, *J. Phys. Chem. A*, 2002, **106**, 6871.
37 G. Parr, L. von Szentpaly and S. Liu, *J. Am. Chem. Soc.*, 1999, **121**, 1922.
38 R.G. Parr and W. Yang, *Density Funtional Theory of Atoms and Molecules*, Oxford University Press, New York, 1989.
39 R.G. Parr and R.G. Pearson, *J. Am. Chem. Soc.*, 1983, **105**, 7512.
40 K. Fukui, *Acc. Chem. Res.*, 1971, **4**, 57.
41 R. Sustmann, *Tetrahedron Lett.*, 1971, **29**, 2717.
42 K.N. Houk, J. Sims, C.R. Watts, and L.J. Luskus, *J. Am. Chem. Soc.*, 1973, **95**, 7301.
43 R. Sustmann, *Pure Appl. Chem.*, 1974, **40**, 569.
44 D.H. Ess and K.N. Houk, *J. Am. Chem. Soc.*, 2008, **130**, 10187.
45 K. V. Gothelf and K. A. Jørgensen, *Chem. Rev.*, 1998, **98**, 863.
46 M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery, T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian-03, Revision B.04, Gaussian, Inc., Pittsburgh PA, 2003.